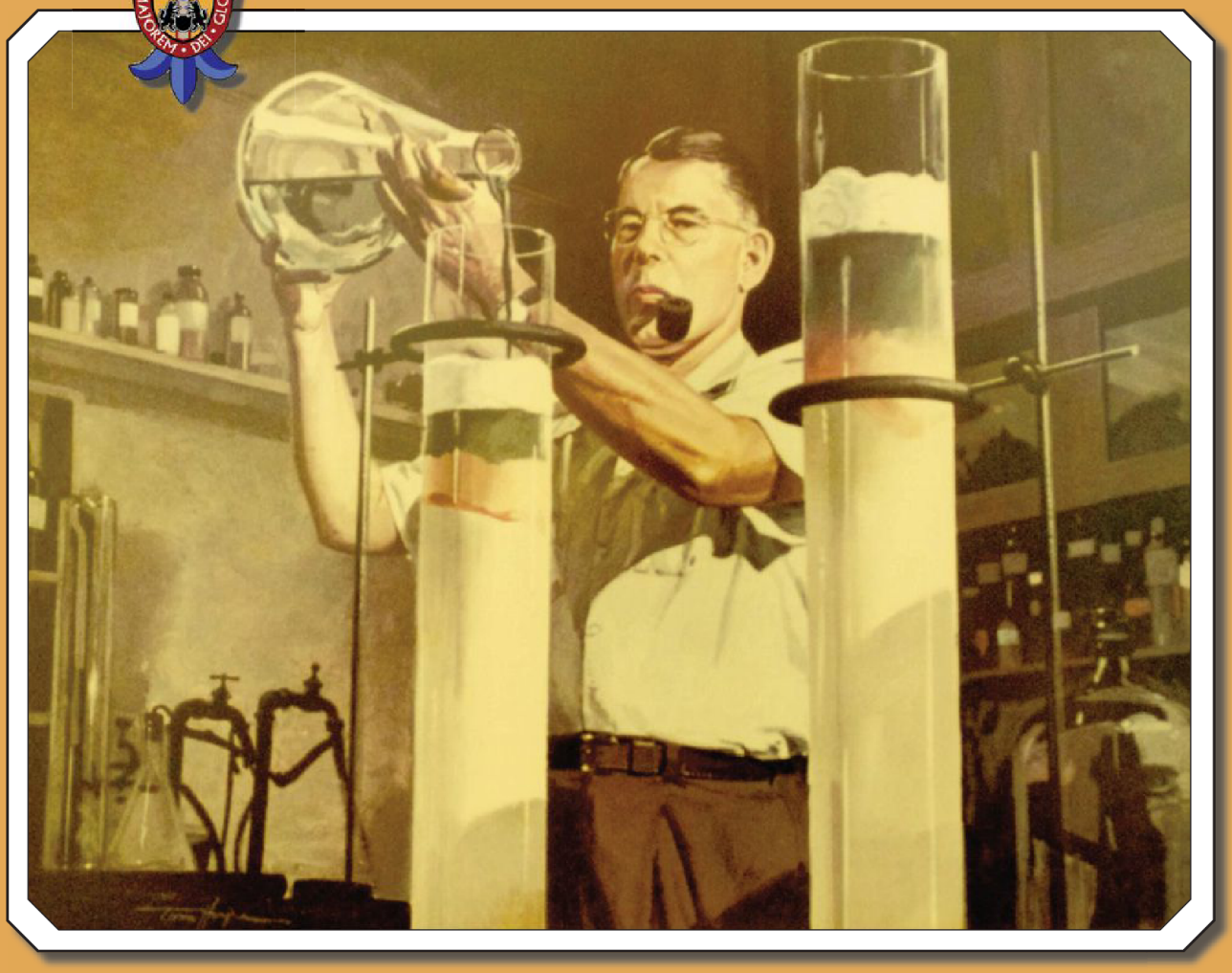
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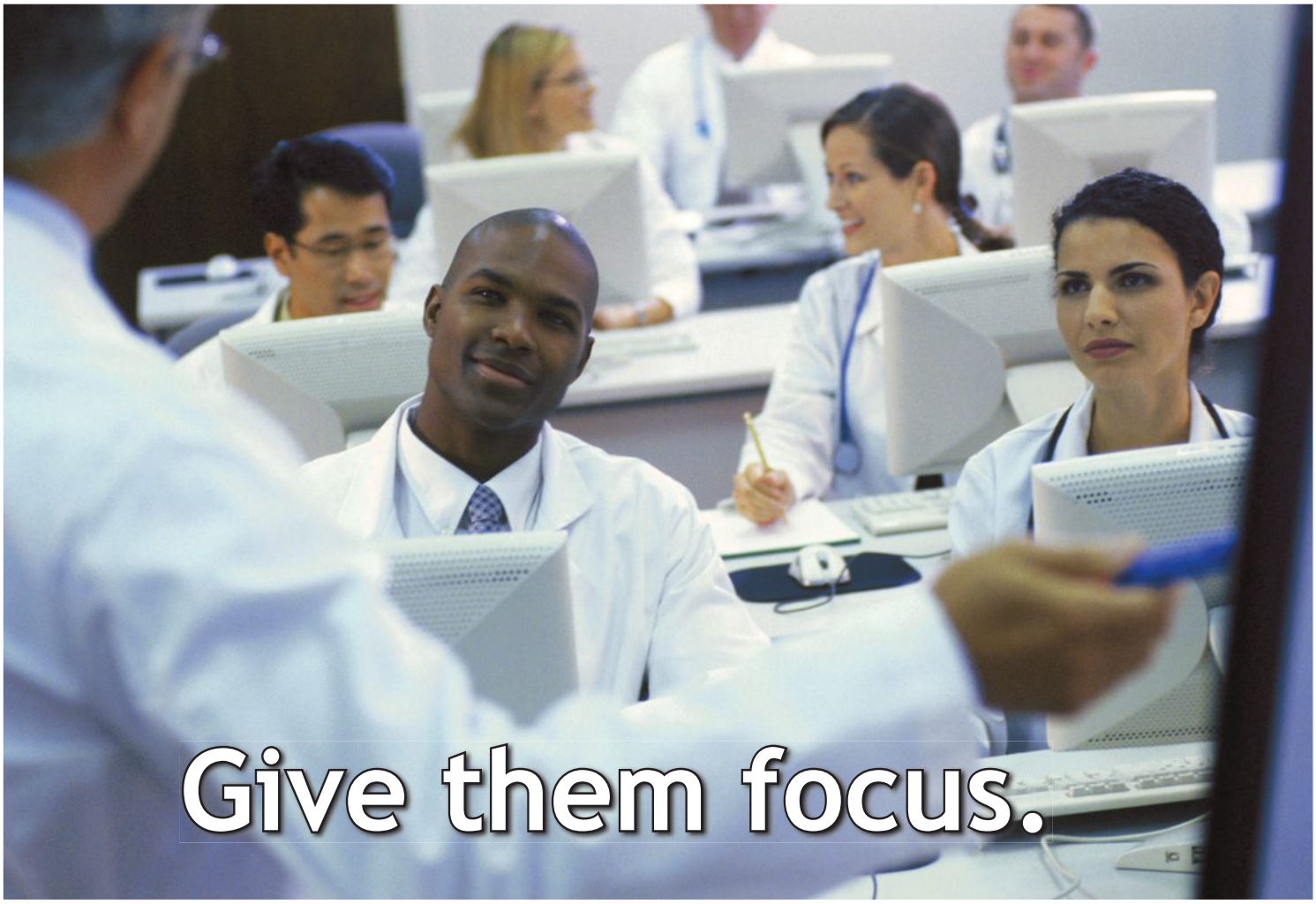
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## *In vitro veritas*



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- ✧ Accountable Care Act Implementation
- ✧ Quality Care: Physician-Owned Hospitals
- ✧ Tort Reform Marches Forward
- ✧ Missouri Delegation Shines at AMA
- ✧ Does Omega-3 Cause Prostate Cancer?
- ✧ PRO/CON: Statin Therapy Over 50
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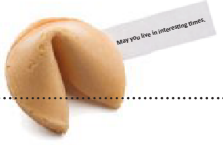
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## ON THE COVER

An image that enjoys a special place in the history of the Edward A. Doisy Department of Biochemistry & Molecular Biology at Saint Louis University School of Medicine shows Dr. Doisy in his lab, in the process of purifying Vitamin K, for which he got the Nobel Prize. It originally appeared in a calendar during the 1950s that honored several Nobel laureates.

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# What I'm Hearing: The Sound and the Fury of Obama-Care (ACA) Implementation

*by John C. Hagan, III, MD*

**It is my hope that the American people and Congress will push the "reset" button and start over on bi-partisan, affordable, implementable, high quality health care for all Americans.**

With increasing rapidity the years of your life will scurry by. You will experience sentinel quotidian events that will score your memory, alter your reckoning of your personal and professional future and recalibrate your value system. You will be invested with a sense of your own mortality so palpable it has a reality of its own. You will wonder who and how you will be cared for if ill, injured, or aged. I share with you a recent epiphany.

Thursday, May 9, 2013 I awoke from a restful sleep almost completely deaf in my right ear. There were no other symptoms such as vertigo, nystagmus, or dizziness. My hearing has been checked regularly over the years. Mild high-tone loss and tinnitus, the result of childhood hunting and target shooting without ear protection, had been very stable. I was startled at how profound the handicap of unilateral deafness was. I could not hear television, radio, converse properly and driving felt insecure. The sense of isolation was profound. My ability to practice medicine was suddenly jeopardized.

I called a group of ENT physicians and was given a same day appointment. An audiology test and exam confirmed a diagnosis of idiopathic sensorineural hearing loss. I was started on oral steroids and improved for 48 hours. The condition then worsened to complete unilateral deafness. I contacted a nationally-known otologist who was at the time playing in a charity golf tournament. He asked me to meet him at his office where he expertly performed a middle ear injection of decadron, a procedure that significantly improves the likelihood of hearing recovery. Indicating that in unusual circumstances an acoustic neuroma can present in such a manner, he recommended a MRI. He called me at home the evening



John C. Hagan, III, MD, FACS, is a Kansas City ophthalmologist and *Missouri Medicine* Editor since 2000. *Contact: jhagan@bizkc.rr.com*

of the test to inform me the results were normal. A week later, after noting a major improvement in my hearing, he performed a second injection. I have recovered about 85-90% of my loss and further improvement continues.

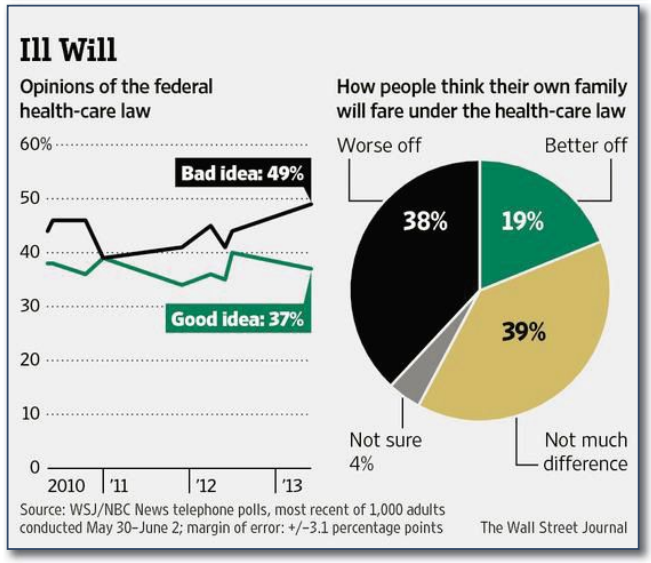
The events of May 9, 2013, and the period thereafter, have made me profoundly grateful for the highly skilled and specialized care I received. I was able to get a same day urgent appointment with an ENT physician; when things worsened I had access to a fellowship-trained, nationally-known otologist who agreed to see me an emergent basis. He was able to offer a unique treatment that improved the chances of a recovery by over 50%. A high quality MRI was promptly scheduled and expertly read and reported to me all in the same day. These competent and compassionate doctors were all on the insurance plan my physician employers offer their staff. My wife and I are Medicare-eligible but we have so many fears and reservations about Medicare and physician access that we pay more out-of-pocket for commercial insurance.

The events of May 9, 2013 have also left me profoundly fearful for the future of American Medicine and the care my wife and I will receive if forced to be insured under Medicare. Things will be much worse if the Affordable Care Act (ACA), aka "Obama-care," is fully implemented. Our concern extends to all U.S. citizens and our nation's present and future physicians. Medicine in the U.S. faces many grave threats.

Many of the drugs, instruments and techniques that are sight/hearing preserving and lifesaving are not available to U.S. physicians due to the ineptitude, uncaring and incomprehensible bureaucracy of the Food and Drug Administration (See "Serious Drug & Device Delay: Thank the FDA," parts I-IV, March/April and May/June, 2013). The power and predation of U.S. trial lawyers has also stifled medication and device development. U.S. companies are moving testing and early marketing to the rest of the developed world where junk lawsuits and vexatious litigation are proscribed by law. In Missouri, millions of tort kings' and queens' dollars have been spent to overturn the highly successful 2005 tort reform law. The thoroughly corrupted "Missouri Plan" for picking judges has denigrated into a conduit into which the trial bar unimpeded invests their advocates and shills onto the seats of the state's most powerful courts (see "Missouri Compromised," Sept/Oct 2013).

The high costs of a medical education, equipping and staffing a medical office, coupled with parsimonious Medicare reimbursement (4% increase since 2000, at present reduced to 2% by the sequestration. Same period medical practice expenses have increased over 20%). Commercial insurance payments are only somewhat

## 1 Picture = 1,000 Words




better. These and other adversities have driven over half of our physicians to become hospital employees. While hospitals are the primary drivers of skyrocketing health care expenditures (See "Bitter Pill," May/June 2013) they have escaped blame and have preferred reimbursement and taxation benefits. Hospitals are the real winners, perhaps the only winners, under the ACA.

The ACA jeopardizes the type of outstanding care that I received during my recent illness. It jeopardizes the quality of care you and I can render our patients. There is $5 billion to $10 billion over 10 years for the thoroughly discredited IRS administrative (FactCheck.org), yet none for funding medical education and training more physicians. The ACA is so ponderous, expensive and byzantine that it is proving difficult, hopefully impossible, to implement. The false promises this President and his supporters offered Americans, notably not having to change physicians and not losing existing insurance coverage are now causing political allies - notably labor unions - to look askance at ACA implementation.

Given the many scandals and self-inflicted wounds this President and his administration have suffered; the growing dissatisfaction with provisions just surfacing from the 20,000+ pages of regulations; it is my hope that the American people and Congress will push the "reset" button and start over on bi-partisan, affordable, implementable, high quality health care for all Americans.

I like the sound of that! MM



# ACA Threatens to Increase Government Involvement in the Practice of Medicine

*by David Pohl, MD*

**As the implementation of the ACA takes shape, physicians should speak up to influence the outcome**

How will the Affordable Care Act (ACA) affect the practice of Medicine? No one really knows since to put it bluntly, as then House Speaker Pelosi did, "We have to pass the bill so that you can find out what is in it." Even George Orwell would have been proud of that bit of double-speak coming from our so-called governmental leadership. This is a bill that will take control of roughly one-sixth of the U.S. economy, disrupt the practice and privacy of medicine's physician-patient relationship, and will become what the government wants it to become since many of the provisions and codicils are not yet written but remain to be determined by a non-elected bureaucracy appointed by the self-anointed experts in health care as determined by our government.

As so many have noted in many other areas of life, "common sense isn't common." There is some hope for the future since challenges to the heavy-handed implementation of the ACA may become the norm. SLMMS, working in conjunction with our state and national organizations, will strive to prevent those portions of the ACA which are antithetical to the proper professional practice of medicine, from taking place.

A central component to the ACA is the formation of the Accountable Care Organization which is meant to be the "cradle to grave" vehicle by which the ACA is doled out. Once all of your patient's care is conveniently and efficiently administered through one government-approved spigot, the easier it will become for the government to determine the flow of the spigot; what benefits are approved to be delivered by the spigot; as well as which patients, which age groups, and which medical conditions are allowed access to the spigot. It would do physicians well to remember that, similar to the fact that we have a legal system rather than a justice system, we also have a government concerned about health costs rather than health care.

The implementation of the ACA continues to be problematic. Take the state insurance exchanges as an example. It was postulated by the administration that every state would want to set up its own exchange in lieu of one run by the federal government. However, several states have set the stage for a challenge to this by not only declining to do so but also to resist the requirement that the federal government has the right to do so. In the recent past, Missouri voted overwhelmingly in favor of pre-empting the implementation of the ACA.

Georgia recently passed a safe harbor bill protecting the medical profession in that state by prohibiting the use of ACA performance standards, administrative



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requirements and payment practices (e.g., withholds) from being admissible in a legal setting as a violation of professional and practice standards (negligence and standard of care). These include in particular so-called quality measures (which often have cost-savings as a component of the measure), readmission rates (over which physicians may have very little control), and hospital-acquired conditions (over which the physician would be penalized for the institutional shortcomings of the admission location) as well as those situations deemed by ACA as "never" events.

That we, as the medical profession in Missouri, should seek introduction of a similar bill in our state legislature will become one more item in the list of actions which SLMMS will help our members achieve. But we will need our membership to become actively involved in communicating with and educating their representatives in order to be successful. However one wishes to term it—"grass roots," advocacy, or involvement—we need an active membership to achieve our common goals.

One of the more surprising comments I heard at the recent MSMA meeting in Kansas City came from one of our physicians in the state legislature who noted that the receipt of more than 5-10 personal letters, phone calls, emails or other contacts by a representative on any given topic is typically considered a huge volume of support. Just imagine what just one contact from one member of each medical practice in the St. Louis community would mean. If each group could have one interested member follow the political climate in which we practice, and take the time to get other group members to pen a short missive, the impact would be truly impressive.

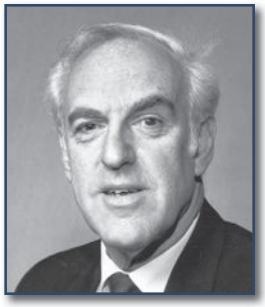
We come to the bottom line. If you want to preserve a profession which continues to look out for the best for your patient and of which you can be proud to represent, then we need your involvement. If you are willing to become a shill for the bureaucracy of government-appointed non-physician boards whose edicts and measures are designed to control health expenditures rather than care for the patient, then go ahead and relax, it's on the way. MM



# Failed Health Care Policies Portend Bleak Future for Physicians & Patients

*by Arthur Gale, MD*

**The number of Massachusetts residents who have financial problems in paying their medical bills is unchanged from what it was prior to the passage of Romney Care.**



Arthur H. Gale, MD, MSMA member since 1976, is a Missouri Medicine Contributing Editor. He practices Internal Medicine in St. Louis.
*Contact: agalemd@aol.com*

Today we see physicians on TV, in newspaper ads, and glossy handouts smiling in their neatly pressed white coats. They all appear to be happy. The reality is quite different. In a 2012 survey of over 13,000 physicians, one of the largest surveys of physicians ever conducted, the Physicians Foundation, a not-for-profit organization, found that most doctors held negative opinions about the present and future state of the practice of medicine.[1]

Some of the key findings are as follows:

- Over three-fourths of physicians surveyed are pessimistic about the future of the medical profession.
- The majority of physicians would not recommend medicine as a career to their children or other young people.
- Over one-third of physicians would not choose medicine if they had their careers to do over.
- Over 60% of physicians would retire today if they had the means.
- In the next one to three years, over 50% of the responding physicians plan to cut back on patients work part-time, switch to concierge medicine, retire or take other steps that would reduce patient access to their services.
- Over 80% of the respondents believe that doctors have little ability to change the system.

This physician discontent is produced to a large extent by failed, unproven government programs that are supported and often led by hospitals, health insurance companies, large corporations, and even some physician professional organizations. The stated goals of these programs are to lower costs and improve quality. Based on the available evidence they will do neither.

Some of the major problem areas to be discussed are: The Patient Protection and Affordable Care Act, Accountable Care Organizations, Hospitals and Hospitals ownership of physician practices, Medicare Advantage, Electronic Medical Records, Hospitalists, Patient Centered Medical Homes, and Wellness programs. When available the views of physicians polled in the Physician Foundation Survey will be presented.

## Patient Protection and Affordable Care Act: aka "Obama Care"

It is still too early to render a final verdict on the Patient Protection and Affordable Care Act (ACA). A law similar to the Affordable Care Act–so called Romney Care-was enacted in Massachusetts in 2008. We can glean some important information from the Massachusetts experience. It serves as a kind of a pilot program for the Affordable Care Act.

The Massachusetts Medical Society conducted a poll of physicians in 2012. Most Massachusetts doctors do not like the Romney Plan. Waiting times are up and costs for patients are up,

and whereas almost 100% of Massachusetts doctors accept Medicare, many doctors have no openings for Romney Care-insured patients.[2]

Another important concern about the Affordable Care Act is that small business owners may drop out of the market deciding that it is too expensive to offer health insurance to employees even with the aid of subsidies. The CEO of the Cleveland Clinic, Delos "Toby" Cosgrove, ominously stated that when employers start checking what it costs to give employees health insurance vs. what it costs to pay a penalty, there could be a domino effect. Employers may choose to pay the penalty thereby ceding health care to the government. Cosgrove predicts that within 10 years 75% of employees will receive health insurance from the government. He thinks this would sound the death knell for employer-based insurance in this country. This is a remarkable statement coming as it does from the head of the Cleveland Clinic, which is often held up as a model for the rest of the country for efficiency and cost control.[3] Another option for employers to evade the expense required by the Affordable Care Act would be to hire more part time workers.

A detailed analysis of Romney Care was published in the *St. Louis Post Dispatch* on March 24, 2013.[4] The article notes that under Romney Care access to health care was achieved, but costs were not controlled. The Boston area remains one of the costliest areas in the country to obtain health care. The number of Massachusetts residents who have financial problems in paying their medical bills is unchanged from what it was prior to the passage of Romney Care. Based on that experience the Affordable Care Act will likely be unable to control high health care costs. A logical question is what good is access to health care if it is unaffordable.

Steven Brill, author of a recent landmark essay in *Time Magazine* on the high cost of health care, also contends that Obama Care will fail because the same players will be running the show as they are now: high cost hospitals, high cost private insurers, and high cost drug and device companies. Without reining in the charges of these major players Brill concludes Obama Care will fail.[5] (*See "Bitter Pill: Analysis of Steven Brill's Time Magazine Article, May/June 2013 by Dr. Gale*) More than half of physicians in the Physician Foundation survey had negative opinions of the Patient Protection and Affordable Care Act.

## Accountable Care Organizations (ACO)

The term Accountable Care Organization (ACO) was first used by a health policy researcher, Elliot Fisher, at Dartmouth Medical School in 2006. The Dartmouth Group has always favored capitation and HMOs to lower health care costs. Fisher, along with MedPac, the influential and the supposedly independent Medicare Payment Advisory Commission, interested Congress in ACOs.

"ACOs became so fashionable among Congressional Democrats it was mentioned in all three draft health care reform bills prepared by the House."[6]

Congress was interested in finding a substitute for the SGR or sustainable growth rate the yardstick by which doctors are paid. The AMA and other medical associations have fought for repeal of the SGR for years. However, be careful what you wish for. ACOs may be worse for doctors than the SGR.

The best way to understand ACOs is to recognize that they are modern-day HMOs. They are the same old wine in new bottles. In the l990s gatekeeper HMOs were supposed to be the solution to America's health care crisis. These HMOs were rejected by the American people. Patients had to get the approval of a gatekeeper primary care doctor before they could see the doctor of their choice. The American public hated the heavy-handed tactics of gatekeeper HMOs, and gatekeeper HMOs quickly disappeared.[7]

But the policy wonks never give up. The ACO is an attempt to form an HMO that will not repeat the mistakes of the 1990s and alienate the public. There will be no gatekeepers. Wary of a consumer backlash, ACOs allow patients to obtain care anywhere they choose even with the most expensive doctors and hospitals even though this undermines the projected cost savings of ACOs.

There have been no pilot projects with ACOs. The Congressional Budget Office estimates that the savings from ACOs would be $1.1 billion over the next five years, but this is insignificant in a total annual Medicare budget of $468 billion.[8] Based on past experience with other kinds of HMOs, it is highly unlikely that ACOs will significantly lower costs. A majority of physicians in the Physician Foundation survey rated ACOs negatively in their ability to control costs.

## Hospitals and Hospital Ownership of Physicians' Practices

The 22,000-word 39-page landmark "Bitter Pill" discusses the high cost of health care and focuses primarily on the outrageously high hospital bills and the "chargemaster," the mysterious method by which hospitals calculate bills, as the main culprits in skyrocketing medical costs.[9]

The author, Steven Brill, believes that currently only Medicare possesses the power to stand up to hospitals and negotiate charges. Supposedly, insurance companies bargain with hospitals over charges, but it's a seller's market

today, and the hospitals are in the driver's seat. Insurance companies need hospitals more than hospitals need insurance companies. If the U.S. is going to get control of skyrocketing medical costs hospitals charges will have to come down to levels approaching those of Medicare. The cover of *Time* magazine shows a picture of a Tylenol pill marked up 10,000%.

Hospitals do not purchase medical practices in order to decrease overall medical spending. They buy them in order to increase market share and enhance their profits Hospitals lose an estimated $150,000 to $250,000 per year for the first three years when they buy medical practices.[10] But that is small change when one calculates the amount of business that doctors refer to hospitals. A primary care physician owned by a hospital refers on average almost two million dollars in hospital charges per year.[11] However, whether the primary care physician was or was not owned, he or she would likely refer same number of patients to the hospital. The extra charge of owning doctors is just passed on to the public.

When hospitals buy physician practices charges go up. A dominant hospital system in the East charged four to ten times the amount local competitors charged for a colonoscopy. A member of a local gastroenterology group said that the day his office was bought out by a hospital system the charges for the colonoscopy performed by the same doctor in the same building doubled. *The New York Times, Wall Street Journal*, and other publications have written about this phenomenon extensively-"same office, same procedure, same doctor and charges double or quadruple."[12] Medicare and other third parties pay physicians who work for hospitals almost double what a physician in an independent private practice receives for the same diagnostic and procedural codes. For example a mid-level office visit in a private physician's office is $69.97. The same visit to hospital-based practice is $124.40.[13]

Medicare started paying physicians owned by hospitals an extra "facility fee" in 2000. Hospitals soon took advantage of this seemingly innocuous clause. Insurance companies followed suit. This paved the way for hospital ownership of physician practices. Now MedPAC, the non-partisan Medicare Payment Advisory Commission, has recommended that this disparity be eliminated.[14] Congress has the final say and hospitals are lobbying vigorously against eliminating this pay differential. But there is enormous pressure on Congress to reduce Medicare costs. If the MedPAC recommendation is implemented hospitals may have to lay off many of their hired physicians.

These policies don't make any sense from the standpoint of lowering overall health care costs. The only way they can be understood is that the hospitals want to eliminate private practice and fee-for-service medicine. Eventually, they want to control how physicians practice and how they are reimbursed. In trying to understand the motives of the so-called experts who have initiated these senseless policies we must never overlook those timeless universal traits of human nature so eloquently described in the plays of William Shakespeare: envy, jealousy, and vindictiveness.

When asked to respond to the statement "hospital employment of physicians is a positive trend likely to enhance quality of care and decrease costs," 74% of the 13,000 physicians surveyed by the Physicians Foundation disagreed. Over 70% of doctors agreed with the statement that hospital employment will erode the physician-patient relationship and quality of care. Surprisingly 62% of the employed doctors do not look upon hospital employment as a positive trend.

## Hospitalists

Like most of the topics already discussed the introduction of hospitalists was intended to lower costs. And like most other policies we've discussed it has failed in its mission. A 2007 report released by the AMA revealed that 64% of hospitalists are subsidized by the hospitals at about $60,000 per year, which means that hospitalists' income is not solely dependent on third party reimbursement as is the case with most U.S. physicians. The average compensation package was $168,000 in 2007.[15] Since that time the average hospital subsidy has doubled and the total compensation package has increased proportionally to about $225,000, depending on the geographic area. Total hospital costs for hospitalist salaries can amount to several million dollars annually.[16]

More importantly, hospitalists don't cut costs. A study from the Annals of Internal Medicine, August 2011, evaluated total costs associated with hospitalists. The study evaluated length of stay, hospital charges, physician visits, emergency department visits, re-hospitalization, and Medicare spending within 30 days after discharge. Although length of stay was reduced slightly, (about a half a day) the cost savings were more than offset by post hospitalization charges.[17] The hospitalist movement is just another way that hospitals can shift costs. The hospitalists saved money for the hospital but overall spending by Medicare was actually increased on patients cared for by hospitalists.

## Medicare Advantage

Medicare Advantage plans started out essentially as Medicare HMOs about three decades ago. Subsequently,

they were called Medicare Plus Choice. And then the name changed again to Medicare Advantage. Medicare Advantage offers Medicare patients extra benefits like dental services, vision care, hearing aids, podiatry, and health club memberships. And they often avoid payment for supplemental policies for Medicare insurance. Advantage plans have grown enormously and cover about 27% of all Medicare patients. In some states membership is significantly higher - up to over 40%.[18] Medicare Advantage plans are heavily marketed by insurance companies. Senior citizens like Medicare Advantage because they are cheaper and offer more benefits. Insurance companies like Humana and United Health Care love them because they have become their most profitable product.

The problem with Medicare Advantage is that it costs U.S. taxpayer anywhere from 7 to 12% more than regular Medicare. Seven to twelve percent may not sound like much, but one research group estimated that the total cost of subsidies to Medicare Advantage or Medicare HMOs over the past three decades amounted to over $282 billion.[19] When Medicare is desperately trying to cut costs, why should it subsidize Medicare Advantage plans? If the government is going to subsidize one group of Medicare enrollees, it should subsidize all of them. Anything else is unfair to the American taxpayer.

CMS, which oversees Medicare expenditures, plans to cut Medicare Advantage over the next few years. The insurance company lobby is fighting tooth and nail to prevent this from happening. Many Members of Congress from both parties are beholden to them. Insurance company lobbyists have mobilized the Medicare population to support Medicare Advantage and members of Congress are afraid to antagonize this huge voting block.

## Electronic Medical Records

EMRs were supposed to save Medicare $81 billion per year according to a 2005 report by the Rand Corporation. The report anticipated that over a 15-year period $150 billion could be saved in outpatient care and $350 billion could be saved in inpatient care. The report was embraced by the Obama administration and Congress. The federal government was encouraged to give billions of dollars in financial incentives to encourage adoption of EMRs.

Now a new report from the RAND Corporation, reported by the *New York Times* in 2013, showed that conversion to electronic medical records has failed to produce *any* savings! In fact there is increasing concern that electronic medical records have actually increased costs by making it easier for hospitals and other providers to bill for services. RAND acknowledged its earlier report was "overly optimistic."[20]

The main beneficiary of electronic health records is the electronic health care industry. Incredibly, the RAND study was paid for by General Electric, the Cerner Corporation, and other companies that gained enormous profits from EMR sales. Cerner's revenue nearly tripled to a projected $3 billion in 2013 from $1 billion in 2005. This is the same kind conflict of interest that occurred when stock and bond ratings companies like Standard and Poor and Moody's gave triple A ratings to worthless subprime loans, which led to the stock market meltdown of 2008.

Not only do EMRs fail to reduce costs, the majority of doctors lose money on them. More than 210,000 physicians have received payments through the government stimulus program. Despite these payments a Health Affairs paper found that only about 27% of practices made money using them. With stimulus grants, that figure jumps to 41%. Smaller offices, those with five doctors or less, struggled the most trying to make EMRs profitable.[21]

Another major problem with EMRs is that physicians have to work longer hours because of dysfunctional software. This is the greatest complaint that I hear from doctors. Either the doctor works longer hours or sees fewer patients.

What about quality of care? There have been studies that show that electronic medical records may actually reduce quality. The majority of mistakes are not technical errors like writing wrong prescriptions but from misdiagnosis. A study of orthopedic surgeons compared handheld electronic medical records with paper records. There were 48 wrong or redundant diagnoses in the computerized record and eight in the paper-based cohort. A 2008 study on the quality of care of more than 15,000 patients with congestive heart failure concluded that electronic health records resulted in little improvement in quality of care. A recent study by a group of Canadian researchers reviewed more than 3,700 published papers on EMR use in primary care. They found no evidence of benefits or drawbacks accruing to patients.[22] A recent 2013 report in *American Medical News* showed that hospital staffs often cut and paste incorrect data. The error then gets propagated virally with each passing day.[23]

Seventy percent of the physicians surveyed by the Physician's Foundation were using electronic medical records. Only one-third felt that it improved quality.

## Medical Homes

Another proposal by the government, the managed care industry, hospitals, and primary care organizations, is the

Patient-Centered Medical Home. Because of the shortage of primary care physicians due in part to professional dissatisfaction, the PTCA utilizes nurse practitioners extensively. This is anticipated to result in improved access and lower costs. They are being widely implemented in the Affordable Care Act and they are required for any organization to be recognized as an ACO. Like just about everything that we have discussed thus far there is no proof that the PCMH improves quality or cuts costs. One observational report in the *Annals of Internal Medicine,* February 5, 2013, evaluated 19 comparative studies of the PCMH. There was no evidence for overall cost savings.[24] Only about one-quarter of physicians surveyed by the Physicians Foundation thought that Medical Homes would lower costs and improve patient access to care.

## Wellness Programs

Wellness programs are an attempt by employers to keep employees from getting sick and thereby avoiding the costs of hospitalization. Some of these efforts are led by insurance carriers. About 30% of businesses with 500 or more employees have various types of wellness programs. Probably the most thorough study on costs savings from Wellness Programs was by BJC, a hospital chain based in St. Louis, and reported in *Health Affairs* in March 2013. BJC has 28,000 employees. Costs of hospitalization decreased by $22 per month, but outpatient costs rose by $19 per month. The conclusion of the study was that the wellness program did not result in significant cost savings.[25]

## Conclusion

When analyzed objectively none of the government proposals to reform health care has been shown to lower costs or to improve quality. These failed strategies will cost billions of dollars. The Physicians Foundation survey has shown that physicians are demoralized and dispirited. A medical profession with poor morale and a dysfunctional health care delivery system do not bode well for three hundred million American patients.

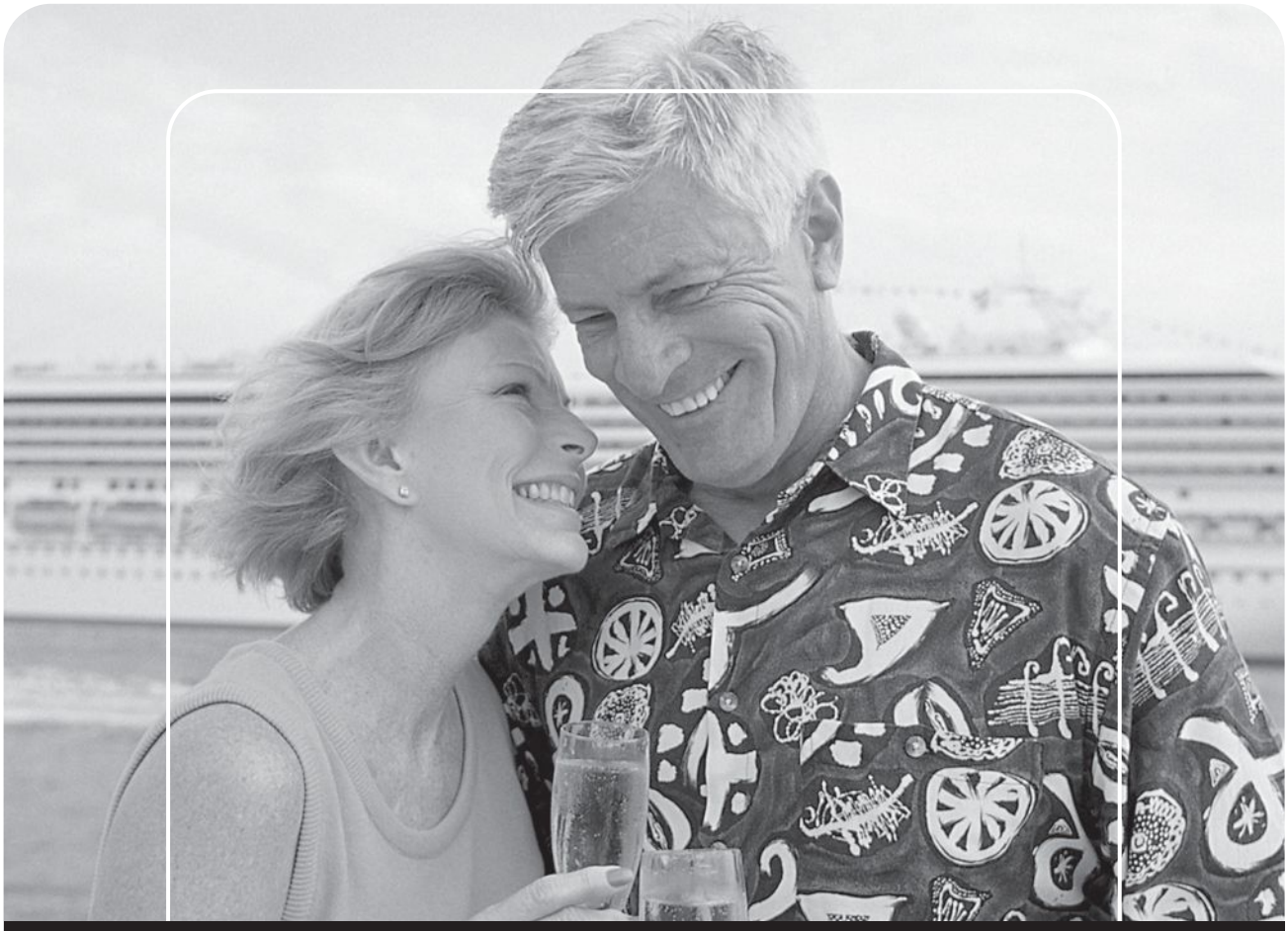
The health care experts believe that eliminating private practice completely will finally bring down health care costs even though all of their own previous efforts over the past three decades including managed care, HMOs, and integrated hospital systems have been failures. Now doctors in small independent private practices are being made scapegoats for the experts' own failed policies. I predict that the experts' new programs will fail just like their former programs because, as noted above, they do not address the real drivers of out of control costs: hospitals, insurance companies, and drug and device companies. Instead the health care experts like the Dartmouth Group mentioned above promote complicated, unworkable, and expensive gimmicks like the Affordable Care Act and Accountable Care Organizations.

Perhaps policy makers might benefit from consulting with and listening to practicing physicians who actually treat patients instead of unilaterally imposing their failed programs on the medical profession and the public. If they did, their programs might be less complex and less wasteful. For sure they couldn't be worse than their current proposals.

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# Physician-Owned Hospitals Seize Their Moment

*by Tanya Albert Henry*

**Supplied with government data ranking them among the best for value of care, doctors at these facilities keep fighting to lift expansion restrictions.**

***Congress already spoke on this issue when it passed a provision to ban self-referral to new physician-owned hospitals. Repealing it would drive up health care costs and will make it hard for full-service hospitals to provide essential public services.***

When the federal government sorted through the first round of clinical information it was using to reward hospitals for providing higher-quality care in December 2012, the No. 1 hospital on the list was physician-owned Treasure Valley Hospital in Boise, Idaho. Nine of the top 10 performing hospitals were physician-owned, as were 48 of the top 100.

With only 238 physician-owned hospitals in the U.S., the facilities said scoring so well on a list with more than 3,000 entries shows the doctor-owned hospitals in a very positive light. The list was released by the Centers for Medicare & Medicaid Services in December 2012 in a report on hospital value-based purchasing.

But the new information comes nearly three years after a section of the Affordable Care Act effectively banned these facilities from expanding and prohibited new majority physician-owned facilities from opening their doors.

"The government says, 'You are the best of the best, but we don't want you to compete in the community.' It's an oxymoron," said Nicholas Genna, CEO of Treasure Valley Hospital. "I would like to see the moratorium on growth lifted, because we are one of the examples of low cost and high quality."

Efforts to lift the 2010 restrictions have proven unsuccessful so far. A lawsuit challenging that portion of the ACA was dismissed by the 5th U.S. Circuit Court of Appeals in August 2012, citing a lack of jurisdiction. Physician Hospitals of America, the trade group representing physician-owned facilities, said it would continue to study its legal options.

Efforts to have Congress repeal what has come to be known as Section 6001 of the ACA also have been unsuccessful. Michael D. Maves, MD, MBA, then-executive vice president and CEO of the American Medical Association, wrote a May 2011 letter to Congress supporting a bill to end the ban on new physician-owned hospitals and lift the expansion restrictions on existing facilities, but the measure went nowhere.

The American Hospital Association and the Federation of American Hospitals continue to back that section of the ACA. Several key lawmakers, including Senate Finance Committee Chair Max Baucus (D, Mont.) and panel member Chuck Grassley (R, Iowa), are in strong support of community hospitals in the debate.

Leaders of physician-owned hospitals, however, said the new government quality figures reinvigorate their quest to persuade lawmakers to overturn that portion of the law.

## Payment Tracking Quality

Medicare's hospital value-based purchasing program aims to start paying facilities based more on the quality of the care they provide, rather than paying solely based on the volume of services. Under the initiative, hospitals will see pay rates increased by as much as 1% or reduced by as much as 2% based on how well they score on process measures, such as the percentage of patients given an

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antibiotic within an hour of surgery. Readmission rates for certain types of conditions and patient experience scores also figure into whether a facility's pay rate increases or decreases.

"With this new data, physician-owned hospitals show very favorably. We will try to use that on the Hill," said PHA President Paul Kerens, senior executive officer of the Kansas City Orthopedic Institute in Leawood, Kan., a physician-owned facility. "It is CMS' own data that [state] we are providing the quality. To me, it doesn't make sense that you say to the best-quality hospital: 'You can't expand.' "

## For Doctor-Owned Hospitals, Medicare Quality Matters

The Centers for Medicare & Medicaid Services has started increasing hospitals' pay by as much as 1% or lowering it by as much as 2% based on how well each facility scores on 12 measures of clinical care, patient satisfaction surveys and readmission rates. Here are the top-scoring hospitals based on the combined results, showing how the hospitals' pay rates will be adjusted. Among the top 10 hospitals, only Marlboro Park Hospital is without physician ownership.

| Hospital | City | State | Change in Pay |
|---|---|---|---|
| 1. Treasure Valley Hospital | Boise | Idaho | 0.83% |
| 2. Lincoln Surgical Hospital | Lincoln | Nebraska | 0.78% |
| 3. Baylor Medical Center at Trophy Club | Trophy Club | Texas | 0.78% |
| 4. Tops Surgical Specialty Hospital | Houston | Texas | 0.75% |
| 5. Marlboro Park Hospital | Bennettsville | South Carolina | 0.74% |
| 6. Baylor Medical Center at Uptown | Dallas | Texas | 0.74% |
| 7. Irving Coppell Surgical Hospital | Irving | Texas | 0.73% |
| 8. Surgical Hospital at Southwoods | Youngstown | Ohio | 0.73% |
| 9. Indiana Orthopaedic Hospital | Indianapolis | Indiana | 0.72% |
| 10. Baylor Heart and Vascular Hospital | Dallas | Texas | 0.72% |

*Source: "Hospital Value-Based Purchasing: The Official Website for the Medicare Hospital Value-based Purchasing Program," Centers for Medicare & Medicaid Services, December 2012 (link); "Medicare Bonuses and Penalties for U.S. Hospitals," Kaiser Health News, December 2012 (link)*

With 30 million people expected to gain health insurance in the years after the ACA goes into full effect in 2014, there is no justification to hold back physician-owned hospitals, said orthopedic surgeon John W. Dietz Jr., MD, chair of the board of managers for Indiana Orthopaedic Hospital in Indianapolis. His hospital ranked in the top 10 of Medicare's value-based purchasing program list.

"We are getting more work done for less cost," he said. "When physicians own and operate the hospital, there is a driving sense of responsibility for the outcomes."

Physician-owned hospitals also can be more responsive, because there are fewer layers of bureaucracy, said Dr. Dietz, a member of the PHA's board of directors. "There is a short path to change. Something can be brought up on the floor at 4 a.m. and changed by 4 p.m.," he said.

For physician-owned facilities that also are considered specialty hospitals — roughly 75% — studies have shown that their level of care specialization helps increase quality and positive outcomes and decrease complications, Dr. Dietz said.

And now new Medicare data show how physician-owned hospitals stack up. "We believe in the power of data," he said.

Still, Dr. Dietz said, it will be a David vs. Goliath battle, with a powerful community hospital lobby intent on keeping the restrictions in place. "We are going up against a machine that generates millions of dollars."

Already there are signs that the growth restrictions are hurting the physician-owned hospital industry. When the ACA was enacted, there were 265 such facilities; now there are only 238. "Many physician-owned hospitals are being poached by competitors because [they] need to expand and can't," said Leslie Fossey, a PHA spokeswoman.

The quality data are telling, said David Hogberg, a senior fellow for health care policy at the National Center for Public Policy Research, a conservative think tank in Washington. But he doesn't see the new information helping get the section of the law repealed.

"Whether or not [the information] is there, it doesn't change the interest of the large hospital associations," he said. "The interests against physician-owned hospitals are not going to change the fight."

### Accusations of Unfair Advantage

For years, the American Hospital Association and the Federation of American Hospitals have raised concerns about the practice of self-referral at physician-owned hospitals and have said these hospitals purposely serve healthier, more profitable patients, leaving sicker, costlier patients for community hospitals to treat.

The AHA said those concerns remain very much at play and that lawmakers need to keep the restrictions on physician-owned hospitals in place.

"Congress already spoke on this issue when it passed a provision to ban self-referral to new physician-owned hospitals," the association said in a statement. "Repealing it would drive up health care costs and will make it hard for full-service hospitals to provide essential public services."

The FAH agreed that Congress should leave the law alone. "Any changes would go in the wrong direction," said Jeff Cohen, FAH's executive vice president for advocacy and public affairs. "Anything they would do would cost the government more money and allow more overutilization."

Cohen noted that the federation does not oppose specialty hospitals, just the concept of doctors referring their patients to facilities in which they have financial interests.

"We are against self-referrals in hospitals," he said. "Hospitals — whether Catholic, community or physician-owned — should be on a level playing field. … We believe in open competition."

Cohen said the ACA has "generous grandfathering" for physician-owned hospitals that were in business before the ACA's enactment. He noted that the law allows them to expand their facilities if there is a demonstrated need for their services in the community.

Physician-owned hospital leaders, however, strongly disagreed with the hospital organizations' arguments against their industry.

Dr. Dietz said it is offensive to hear opponents imply that physician-owned hospitals are performing unnecessary surgeries. A 2008 Robert Wood Johnson Foundation study found that physician referrals to facilities in which the doctors have an ownership interest is "becoming increasingly common and not always medically appropriate." But the report went on to say that although evidence suggests self-referral leads to increased utilization, there is "insufficient evidence to determine whether this increased usage reflects doctors meeting an unmet need or ordering clinically inappropriate care."

"We took an oath," Dr. Dietz said. If the surgeries were unnecessary, he added, medical liability attorneys would be on their doorsteps. Insurance companies scrutinize surgery decisions and would steer away patients if unnecessary procedures were being ordered, he said.

"They are not. They are steering them toward us because of cost efficiencies," he said.

Kerens said physician-owned hospitals in the U.S. accept Medicare and Medicaid and perform charity work in their communities.

"If you look at the data, we do not cherry-pick," he said. "Physician owners started getting into the hospital business to provide better patient care and provide efficiencies of care. They are not in it for the money."

## Dreams of Expansion Deferred

Despite what they see as a real need for them to expand their services, physician-owned hospital executives said the ACA sets the requirements hospitals first must meet so high as to be unattainable.

"It was a sham," said Tony Wahl, CEO of Texas Spine & Joint Hospital in Tyler. "In reality, it is too onerous."

Because of the ACA, Texas Spine & Joint was unable to complete a $37 million expansion it had in the works. It spearheaded the unsuccessful court challenge to the statute that was thrown out in August 2012.

"It is a travesty to not be able to grow. There is a serious demand for services here," he said. "My hope is someday quality will prevail in Congress. No matter what the ownership is — whether it is a community hospital, investor-owned or physician-owned — quality should dictate what services are provided."

When the ACA was enacted, Dr. Dietz's hospital in Indianapolis had invested $27 million in a new facility that was under construction. It was able to open as a surgery center, but that necessitated closing inpatient beds at the main hospital, "which is sad," he said. He said the main facility now is at full capacity three to four days a week.

Treasure Valley in Idaho also had planned to add more beds and procedure rooms before the ACA became law. Instead, the hospital will spend $10 million to revamp the 15-year-old facility and will add new observation rooms in the recovery area.

"We plan on being here for a long time," said Genna, the CEO. "The fact that we can't go and build a high-quality and low-cost facility for our community is a disservice. But we can continue to provide care and do."

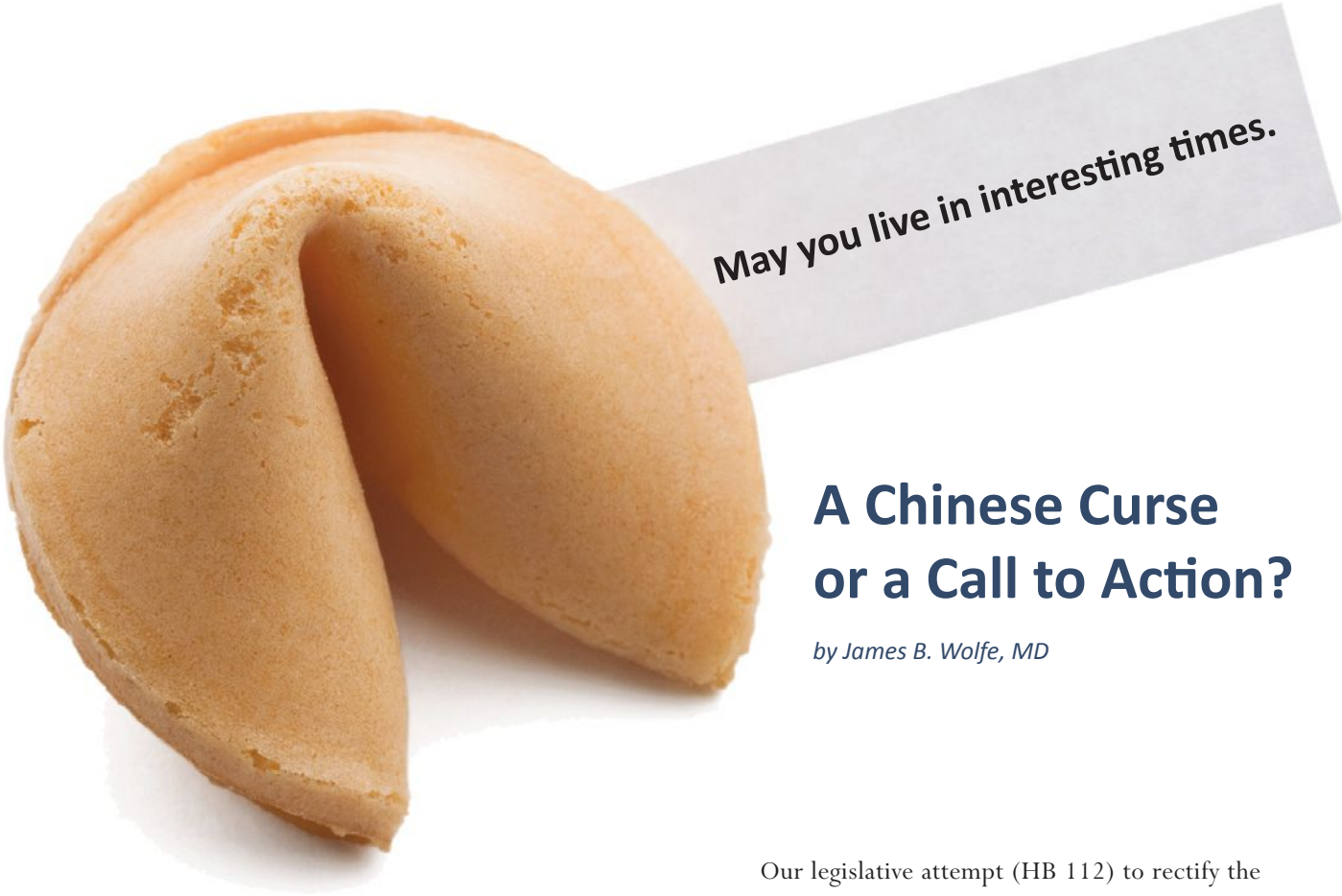
Robb Linafelter, CEO at Lincoln (Neb.) Surgical Center, said the percentage of population growth and the projected patient numbers that facilities must demonstrate before they are allowed to expand under the ACA are "outlandish."

When legislators look at the section of the ACA dealing with physician-owned hospitals, "our hope is at least existing facilities can grow and expand," Linafelter said. His facility, which ranked in the top 10 on the Medicare value-based purchasing program list, is seeing growth in demand, as is the entire Lincoln market.

"Physicians need to continue to stand up for what they believe in," he said. "That is why we have physician-owned hospitals. They built the hospitals to control their own destiny." MM




"As physicians, we have so many unknowns coming our way…
One thing I am certain about is my malpractice protection."
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# A Chinese Curse or a Call to Action?

*by James B. Wolfe, MD*

## We cannot expect to win the fight if we are not willing to fight the fight.

"May you live in interesting times" is an old Chinese Curse. One can certainly argue that someone or something has placed this curse on the House of Medicine. As I noted in my inauguration speech in April I believe that the Affordable Care Act is going to have profound effects on the practice of medicine for many years to come. In addition, the Missouri Supreme Court ruling in August 2012 on Tort Reform increased the stormy seas Missouri physicians are facing.



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Our legislative attempt (HB 112) to rectify the Supreme Court ruling fell short in the waning days of the state legislature despite the fact that the Republican leadership was in favor of our legislative fix. The death of the legislation occurred in the Senate for at least three reasons:

1. Senator Bob Dixon (R - Springfield), Chair of the Senate Judiciary Committee, would not push the Senate version of our bill (SB 105) out of his Committee early in the legislative session.

2. Democrat Senators, especially from St. Louis, were able to mount a short but successful filibuster late in the legislative session.

3. The Republican leadership decided not to bring the bill back up for further discussion during the last week of the session so that other "pressing" legislation could be completed.

It should not surprise anyone that our Tort Reform legislative fix fell short this year. After all, it took MSMA three years to get the Tort Reform legislation passed almost a decade ago (in 2005)! We were then aided by the fact that the public and legislators could see the devastating effects the malpractice insurance crisis was having on Missouri medicine. At one point

there were very few neurosurgeons left practicing in Kansas City, Mo.; they had moved their practices to Kansas City, Ks.

Fortunately or unfortunately, today we have no such conditions. Since we are not presently facing a crisis, the state legislators are less likely to act. A former state legislator once told me that they are unlikely to act on a thorny issue unless there is an imminent crisis.

Given the facts it is quite apparent that a sustained full press by all Missouri physicians will be necessary if we are to succeed against our opponents. The effort cannot wait until the legislative session starts. Although our MSMA staff is already at work on the issue for the 2014 legislative session, Missouri physicians, individually, need to address the issue with their legislators NOW and continue to communicate with them until the legislation becomes law. This is particularly important for physicians whose Senator's names appear at the bottom of the article.

I realize that the majority of Missouri physicians are not independent practitioners, and as such, are less likely to know what their malpractice premiums are. Tom McNeill, who heads our MSMA Insurance Agency, recently indicated that in the nine months since the Supreme Court ruling no malpractice insurers have raised rates on policy renewals. Obviously, the first time a jury awards a large noneconomic judgment, rates will increase quickly. Depending on the frequency of these large awards, we could also, once again, see an exodus of malpractice companies from Missouri. This exodus could be accentuated by the fact that as more independent practitioners become employed, the total premiums written statewide will probably decrease since many of the larger health systems are self-insured.

I appreciate how busy Missouri physicians' schedules are. Nevertheless, we cannot expect to win the fight if we aren't willing to fight. As individuals we need to become more active in the political process. We must get to know our local legislators on a first name basis; we must contribute to their campaigns early. We, our spouses, and our family members need to become volunteers for the local legislators. MSMA provides an excellent opportunity to lobby our state legislators through the "Physician of the Day" program in the Capitol. Utilizing this program you can make appointments with several legislators while you provide medical care for the legislators and their staff. Your MSMA MMPAC and lobbyists would certainly welcome your support.

Remember, united we stand and divided we fall! Let us create some interesting times for malpractice attorneys! MM

**This is YOUR CALL TO ACTION!!**
**The Baker's Dozen of Senators who need enlightenment on Tort Reform are:**

- Senator Ryan McKenna (D, Jefferson County)
- Senator Jamilah Nasheed (D, St. Louis)
- Senator Kurt Schaefer (R, Columbia)
- Senator Eric Schmitt (R, Kirkwood)
- Senator Scott Sifton (D, South St. Louis County)
- Senator Gina Walsh (D, North St. Louis County)
- Senator Chappell-Nadal (D, North St. Louis County)
- Senator Kiki Curls (D, Kansas City)
- Senator Bob Dixon (R, Springfield)
- Senator Jason Holsman (D, Lee's Summit)
- Senator Jolie Justus (D, East Central MO)
- Senator Joe Keaveny (D, St. Louis)
- Senator Paul LeVota (D, Kansas City)

# Missouri Delegation Takes Top Spots at AMA Meeting

*by the Missouri Delegation to the AMA*





Missouri leaders take center stage at the AMA meeting.

Top, from left, Edmond Cabbabe, MD, David Barbe, MD, and Elie Azrak, MD.

Bottom, Dr. Barbe congratulates Regina Benjamin, MD, Surgeon General of the United States.



Ted Groshong, MD, Columbia, MSMA member since 1976, is a pediatrician and a Missouri Delegate to the AMA.
*Contact: GroshongT@health.missouri.edu*

Your Missouri Delegation to the American Medical Association shined at the162nd meeting of the AMA House of Delegates held in Chicago last month.

All of us in Missouri are excited to welcome the re-election of David Barbe, MD, Mountain Grove, to the position of Chair of the AMA Board of Trustees, which is responsible for carrying out AMA policies for the House of Delegates. Dr. Barbe is a former President of MSMA, and just completed his first term on the 21-member Board (16 of whom are elected). Congratulations to Edmond Cabbabe, MD, St. Louis, who was elected to the presidency of the AMA Foundation. Also, St. Louis physician Elie Azrak, MD, served on the AMA's Reference Committee B, covering legislative issues.

There were a number of major issues in medical education that were addressed by the House. Well stated by Charles Van Way, MD, Kansas City, in the May/June issue of *Missouri Medicine*, we have moved from a serious issue to a crisis in physician workforce. While the number of graduates of U.S. allopathic and osteopathic medical schools has been rapidly increasing, the number of residency positions has barely budged. This year, at least 500 graduates, many with very large debt, were unable to achieve GME positions. Neither the Center for Medicare and Medicaid Services, nor the legislature, has been willing to step forward to solve the problem. The AMA House passed a resolution that the AMA become more aggressive in attempting to obtain support from multiple sources in order to increase GME positions. It was clear that the House expects some kind of action before the next annual meeting.

A second issue of importance to Missouri physicians is the whole area of maintenance of certification (MOC), and the national effort by the American Board of Medical Specialties to link this with maintenance of

licensure. Both this issue and the increasing MOC requirements, resulted in a resolution that MOC examinations be transparent, that those Boards show evidence of it being effective in improving the quality of physician performance, and that the exams be evidence based. The AMA is to work with that Board to try to minimize the multiple exams individuals are having to take (as required by cardiologists who have to pass boards in Internal Medicine, Cardiology, Invasive Cardiology, Echocardiography, etc.), as well as the major costs in time taken from patients, in travel, and in payments to the Boards. The AMA is to report back to the House on progress in solving these problems.

Additional important actions included increasing our efforts to convince Congress to roll back scheduled doubling of interest rates for student loans, and a request that the ACGME use evidence based approaches to any revision of resident duty hour rules.

AMA advocacy is central to our mission of representing the needs of our patients, and supporting physicians. For example, the House supported specific guidelines for invasive pain management procedures for the treatment of chronic pain, including procedures utilizing fluoroscopy. Those guidelines emphasized that physicians must supervise other health professionals who may be involved in these procedures. Additionally, as health care in teams is being increasingly encouraged, it is essential that physicians lead those teams.

The AMA will intensify its efforts to improving the flawed portions of the Affordable Care Act (ACA), including the lack of any provisions dealing with the SGR, tort reform, and the Independent Payment Advisory Board.

All of us are concerned with what the implementation of ICD-10 will mean for our practices. This includes the major expense that it will require, and in particular, a potential deleterious effect on those in solo practice and in small groups. The AMA will continue efforts to help Congress understand the lack of benefit of this program, and at the very least, will try to slow down its implementation and to ameliorate the penalties associated with it.

Many physicians have been bombarded by pharmacies calling offices to request information on the diagnosis and medical management of patients. This is both time consuming and intrusive. The AMA is working to help eliminate this practice.

It is clear from this meeting that the AMA is committed to preserving diversity of practice styles. While there appears to be an impetus from the government to force physicians into large group practices, to be employed by hospitals, or to join government entities, we still need to preserve private practice as a choice, and continue to advocate for fee for service.

Among the most important and timely resolutions passed was a call to petition the Center for Medicare and Medicaid Services (CMS) to amend recovery audit contractor (RAC) rules, to prevent the RACs from using extrapolation to determine overpayment amounts to be recovered from physicians unless overpayments were previously documented or educational intervention failed to correct payment errors.

In an effort to curb the significant problem of work-related abuses of IMG physicians working under the Conrad-30 program, the House also called for AMA policy to continue to monitor legislations and provide support for improvements to the J-1 Visa Waiver program, to encourage IMGs to consult with their state medical society on work-related abuses, and to consider requesting assistance from the AMA if needed.

In addition, our AMA House of Delegates resolved to continue to assist states in opposing legislation that would allow for the independent practice of certified registered nurse practitioners, and assist state medical societies and specialty organizations in their efforts to define the valued role of mid-level and other health care professionals within a physician-led team, and actively oppose health care teams that are not physician-led.

There continues to be great concern that the use of electronic record keeping will interfere with patient-physician relationships. Clearly there are connectivity issues between EHRs themselves and third party carriers, including Medicare and Medicaid. While telemedicine expands many security issues remain in all electronic communication, while the expansion to mobile devices creates a need for guidelines to secure the safety of portable applications also. Documentation guidelines are needed to be developed together with AMA and CMS, to outline appropriate use of existing documentation without the fear that "cutting and pasting" could be misconstrued as fraud in the eyes of CMS.

With the advent of "medical teams," guidelines or model designs are needed to insure physician leadership. Of great concern is the increasing use of EMTALA to pressure those physicians serving on "call" lists to see increasing numbers of patients as part of their medical staff obligation. The increasing numbers of aging patients necessitates that geriatric care is a priority among

physicians, while barriers to care need to be removed i.e. excessive documentation requests to secure diabetic supplies, with the burden being places on physicians.

Resolutions on Constitution and Bylaws and the Council on Ethical and Judicial Affairs (CEJA) are often greeted with yawns. However, there was a little excitement from reports from CEJA. Guidelines which are put forward by this Council are often given biblical significance by institutions. There was considerable controversy about a report on the use of conscience in medical practice. Conscience involves morals, religion, personal convictions, and degree of commitment. One would think these would not be controversial. However, due to the complex and individual nature of this issue, it was felt by the House that further study was required. The second CEJA report referred back for additional study was one on pharmaceutical gifts. CEJA considers drug samples to be gifts. Conversely, as they are provided to patients without charge…maybe not.

A myriad of resolutions pertaining to the areas of science and technology were brought to the House of Delegates, many of which stimulated robust discussion. Of note, the House voted to advocate for state Medicaid reimbursement of neonatal male circumcision following recommendations set by the American Academy of Pediatrics in the fall of 2012. Additionally, the House voted to support mechanisms for the education of hairdressers and barbers on skin examination to encourage early skin cancer referrals to qualified health care professionals This stemmed from a resolution brought forth by the Resident and Fellow Section. In regards to the lifetime deferral on blood and tissue donations from men who have sex with men, the House decided that such lifetime deferral was no longer supported by scientific evidence and that deferral periods should be rational, scientifically-based, and stratified according to specific risk levels. One of the more controversial topics in the Science and Technology Reference Committee was introduced by the American Congress of Obstetricians and Gynecologists, advocating for over-the-counter sales of oral contraceptives (OCPs). After lengthy debate, the House decided that the topic was complex and required continued study.

The House voted to encourage increased dental coverage for children with orofacial clefting and fertility preservation for young patients with cancer.

There was considerable concern that managed care fees may drop to the level of fees paid by Medicare, and that the AMA should take leadership in maintaining them at a substantially higher level, and that insurance companies remove patient satisfaction surveys and quality parameters as criteria for physician payment. Additionally, there were concerns raised that new code edits that bundle evaluation and management codes will decrease childhood vaccine rates. There was considerable support to make observation status count towards the three-day Medicare Part A requirement and also to reduce the three day requirement.

Once again, the AMA has decided not to increase dues. The AMA has remained financially strong, even though dues have not been increased since 1994.

For the last 10 years there has been discussion about ending the interim meetings that are held in November of each year. The purpose of these meetings, begun in 1945, is advocacy. Both in order to provide financial savings, and to enhance the National Advocacy Conference held each year in Washington, the House has pressed to go to just the two meetings. Recently it was suggested we stay at three, but change the content of the interim meeting. After considerable discussion and argument, it was agreed to keep the National Advocacy and Interim meetings, and quit debating the issue. This does not preclude altering the structure.

The Medical Student Section plays a vital role in the House of Delegates. Nathan Nolan, a second-year student at the University of Missouri submitted the following comments from the student perspective:

Though it is important to watch the MSS resolutions as they mature and move through the HOD, several other resolutions had the attention of students.

A significant issue facing medical students is student loan burden. This, coupled with the recent increase in unmatched graduate medical students, has been a cause for much anxiety. In Reference Committee C's report were a couple resolutions that addressed some of these fears. The resolution: Support For Quality In Graduate Medical Education, expressly supports the exploration of evidence-based approaches to enhancing GME funding. An additional recommendation was put forward that the report on alternative funding models for GME be presented at Annual 2014. Finally, but still very important to students was an effort to reduce the loan burden medical students will face with the imminent scheduled increase in interest rates on government loan. Student loan debt is ballooning and resident job opportunities are diminishing. The passing of these resolutions signifies the AMAs commitment to helping us tackle this daunting issue. MM

# The Missouri Honor Fund at the AMA Foundation Helps Free Clinics in Missouri

*by Edmond Cabbabe, MD*

The Missouri Honor Fund is more than halfway to reaching $250,000, the level where the fund will start supporting grants to physician-led free clinics in Missouri. We need to raise $105,000, and we need your help.

Missouri has several physician-led free clinics that provide care to people without insurance and those who are underinsured. An estimated 29 million Americans will still be uninsured when the Affordable Care Act is completely in place. These clinics need our support to help them care for these patients.

Several years ago, the AMA Foundation launched the Uniting for the Future of Medicine campaign. Among its achievements was the establishment of endowed funds, known as Honor Funds, which are held in perpetuity by the AMA Foundation. Several state delegations and other physicians joined in this effort by establishing Honor Funds named after their own states, groups, or individuals.

The first ten donors of $10,000 or more to establish a particular Honor Fund decide how to direct the fund's support. Typically the state honor funds choose to provide medical student scholarships or grants to free clinics. Because the Missouri State Foundation annually awards 30 scholarships to allopathic and osteopathic students, the Missouri Honor Fund has been designated to provide annual grants of $10,000 - $25,000 to free clinics.

Our fundraising efforts so far have raised more than $145,000, but we still need your support to reach our goal.

One way to help raise support for this special endowment fund, besides writing a personal or a business check, is by making a presentation about the fund during a hospital medical staff meeting. For example, SSM DePaul Health Center Medical Staff made a group contribution of $5,000. Supporting the Missouri Honor Fund is a win-win situation where hospital medical staff funds can make an impact on some of our state's most vulnerable patients.

You may also connect the AMA Foundation with companies you do business with. Your relationships and contacts can be a valuable resource.

I am happy to provide information and handouts about the AMA Foundation and the Missouri Honor Fund.

Every donation makes a difference and brings us closer to our goal of awarding grants. Donors of $1,000 or more will be recognized in the AMA Foundation publications and on signage at the AMA Annual and Interim Meetings.

Let's take advantage of this opportunity to serve our uninsured patients in Missouri. Thank you for your help!

Contact AMA Foundation Development and Planned Giving Director Anne Smith at anne.smith@ama-assn.org or call 312-464-5852, if you wish to make a multi-year pledge.

Make checks payable to AMA Foundation and include Missouri Honor Fund in check memo. Mail to: AMA Foundation, 515 N. State St., Chicago, IL 60654 MM



Edmond B. Cabbabe, MD, FACS, MSMA member since 1979, is President of the AMA Foundation. He is a Clinical Professor of Surgery at Saint Louis University School of Medicine and Chief of Plastic Surgery at St. Anthony's Medical Center. He is Chairman of the Missouri Delegation to AMA House of Delegates.
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# CORRESPONDENCE

## One Health = One Great Issue!

On behalf of my One Health Initiative (OHI) Autonomous pro bono team colleagues Bruce Kaplan, DVM, Thomas P. Monath, MD, Jack Woodall, PhD, Lisa A. Conti, DVM, MPH and myself, we greatly appreciate your visionary May/June 13 issue of *Missouri Medicine* on One Medicine [commonly referred to as One Health]. Drs. Kaplan (a veterinarian), Monath (a physician), Woodall (a biomedical research scientist), Conti (a veterinarian) and I manage the One Health Initiative website www.onehealthinitiative.com, designed to promote and distribute all pertinent U.S. and worldwide One Health information, publications, and upcoming events. This issue and articles from *Missouri Medicine* were posted on our website in our publications section.

"The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment. The synergism achieved will advance health care for the 21st century and beyond by accelerating biomedical research discoveries, enhancing public health efficacy, expeditiously expanding the scientific knowledge base, and improving medical education and clinical care. When properly implemented, it will help protect and save untold millions of lives in our present and future generations."

A recent publication by the OHI team essentially demonstrates the crucial importance and exponential expansion of the One Health international movement over the past several years www.solutions-site.org/node/875.

Physicians, veterinarians and all health scientists should join forces in a "call to arms" for implementing One Health for the sake of human and animal welfare now and for civilization's posterity. Indeed, there is an obvious critical need for One Health!

*Laura H. Kahn, MD, MPH, MPP*
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*Princeton University*
*Co-Founder, One Health Initiative*
*www.onehealthinitiative.com*
*Columnist, Bulletin of the Atomic Scientists*
*www.thebulletin.org*

## In Memoriam

- Joseph Giangiacomo, MD, 71, Columbia, MO, Ophthalmology, March 12, 2013
- Peter C. Boylan, MD, 77, Prairie Village, KS, Orthopedic Surgery, April 20, 2013
- J. Richard Green, MD, 95, Independence, MO, General Surgery, March 14, 2013
- Hugh G. Harris, MD, 75, Lebanon, MO, Orthopedic Surgery, March, 23, 2013
- Warren M. Lonergan, MD, 97, St. Louis, MO, Internal Medicine, February 26, 2013
- Ira C. Gall, MD, 84, St. Louis, MO, Obstetrics & Gynecology, March 29, 2013
- Charles H. Nicolai, MD, 91, St. Louis, MO, Urology, May 31,2013
- George Sato, MD, 90, St. Louis, MO, Pediatrics, February 5, 2013
- David L. Straub, MD, 72, Joplin, MO, Allergy & Immunology, July 5, 2013
- John B. Summers, MD, 90, St. Louis, MO, Pediatrics, June 12, 2013
- Mary Lou W. Thomasson, MD, 86, St. Louis, MO, Radiology, February 20, 2013
- Sharon E. Waggoner, MD, 91, St. Joseph, MO, Family Practice, March 15, 2013
- Francis S. Walker, MD, 86, St. Louis, MO, Neurological Surgery, March 30, 2013

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# Do Omega-3 Fatty Acids Cause Prostate Cancer? NO!

*by James J. DiNicolantonio, PharmD, Mark F. McCarty, BA, Carl J. Lavie, MD & James H. O'Keefe, MD*

**A more thorough overview of the pertinent literature suggests that increased omega-3 fatty acid consumption does not increase prostate cancer risk, and notably decreases prostate cancer mortality.**



James J. DiNicolantonio, PharmD, is with the Mid America Heart Institute at Saint Luke's Hospital, Kansas City and Wegmans Pharmacy, Ithaca, NY. Mark F. McCarty, BA, is with NutriGuard Research Inc., Encinitas, CA. Carl J. Lavie, MD, is at John Ochsner Heart and Vascular Institute at the University of Queensland School of Medicine, New Orleans and Pennington Biomedical Research Center, Baton Rouge, LA. James H. O'Keefe, MD, (above) MSMA member since 2003, is with the Mid America Heart Institute at Saint Luke's Hospital and University of Missouri-Kansas City, Kansas City.
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There has been recent controversy as to whether fish oil increases the risk of prostate cancer. The concern stems from a paper published recently by Brasky and colleagues concluding that increased blood levels of long-chain omega-3 in plasma phospholipids are associated prospectively with an increased risk for total as well as high-grade prostate cancer.[1] They reached this conclusion based on their own retrospective analysis of serum samples and data derived from the SELECT trial, as well as a meta-analysis of previous pertinent prospective epidemiological studies. The authors speculate that this finding may reflect a pathogenic role for fish oil omega-3s in the induction of prostate cancer. Widespread publicity given to this speculation through the popular media has triggered both consternation and skepticism among the public.

It must be emphasized that this study cannot prove that fish oil causes prostate cancer, as it is observational; it was not a controlled trial in which patients were randomized to receive fish oil supplements or placebos. Furthermore, dietary consumption of fish or fish oil was not assessed in this study, so, even as epidemiology, it cannot establish an association between fish oil consumption per se and prostate cancer risk. Rather, it only establishes a correlation of prostate cancer risk with omega-3s in plasma phospholipids. Whether this correlation reflects a pathogenic role for omega-3s is hypothetical, and there is considerable reason to believe that this hypothesis is incorrect. Conceivably, if their observation proves to be confirmable in subsequent research, the modest elevations of plasma phospholipid omega-3s observed in subjects who went on to develop prostate cancer may reflect some metabolic factor influencing omega-3 partitioning and/or oxidation that also influences prostate cancer induction.

It should be noted that the test used by Brasky and colleagues to assess "omega-3 status" – plasma phospholipid omega-3s – is not the most accurate way to assess long-term omega-3 dietary intake. Rather, the percentage of EPA + DHA in erythrocyte membranes as defined by Harris as the "omega-3 index,"[2] is more useful in this regard. The parameter measured by Brasky et al. is highly susceptible to day-to-day variation in omega-3 fatty acid intake, rendering it less than optimal as a surrogate for the characteristic omega-3 intakes or tissue levels of the subjects studied.

More importantly, a substantial number of epidemiological studies, both prospective and case-control, have previously examined the association between fish or fish oil ingestion and prostate cancer risk, and these findings clearly do not

incriminate long-chain omega-3 ingestion as factor in prostate cancer induction.[3-9] A recent meta-analysis of these studies indicates that fish consumption has a null or slightly protective impact on prostate cancer incidence, but is strongly protective with respect to prostate cancer mortality.[4] Moreover, the limited prospective epidemiology that has evaluated the association of fish oil supplementation with prostate cancer risk – including one study by Brasky's own group – does not provide any grounds for concern in this regard.[3] With respect to patients who already have prostate cancer, frequent fish consumption has been associated with improved survival.

Prior evidence has shown that patients with a higher mean baseline blood level of omega-3 fatty acids are at a lower risk of cardiac sudden death.[10] Indeed, one study found that relatively high omega-3 blood levels (5.63% and 6.87%) were associated with a 72% and 81% lower risk of sudden death, respectively, compared to patients with a mean omega-3 blood level of 3.58%.[10] Brasky and colleagues report a 43% increased risk of total prostate cancer with an omega-3 blood level $>$ 5.31% vs. $<$ 3.68% (hazard ratio [HR] 1.43, 95% conference interval [CI]: 1.09-1.88, p=0.007).[1] Hence, even in the unlikely event that Brasky and colleagues are correct in their speculation that omega-3 increases prostate cancer risk, one would need to balance a 43% increased risk of prostate cancer associated with replete omega-3 status, against a 72% higher risk of sudden cardiac death associated with low omega-3 status.

If fish omega-3 did indeed boost prostate cancer risk, then populations with high omega-3 fatty acid intakes could be expected to have a relatively high risk for prostate cancer; this does not seem to be the case. The intake of fish in Japan is one of the highest in the world,[11-13] being around eight times more than that of American men,[2] and yet the age-adjusted mortality from prostate cancer in Japan was approximately seven times lower than that in the U.S. in the 1950s.[14] Additionally, omega-3 fatty acid levels in red blood cells are approximately 8 to 10% in Japanese patients,[15] around twice that of those in the combined cancer group (4.66%) and controls (4.48%) in the paper by Brasky and colleagues.[1] Thus, the mean omega-3 fatty acid blood levels in the Brasky study are rather low from the standpoint of cardiovascular (CV) protection, and only differed by 0.18% in cases vs. controls - a negligible difference from a clinical perspective.

The very high omega-3 intake of the traditionally-living Inuit, evoked as a likely reason for their low risk for CV disease, first brought omega-3 nutrition to popular attention several decades ago. Less well known is the fact that the Inuit were also at very low risk for prostate cancer incidence and mortality.[15, 16]

Japanese men have a two-fold higher serum level of omega3-fatty acids than whites and Japanese Americans in the United States (U.S.),[11] and coronary heart disease in Japan is about half as common as in the U.S.[17] Contributing to the evidence that a higher omega-3 intake is associated with a reduction in coronary heart disease is JELIS, a randomized controlled trial which showed that adding 1.8 grams of eicosapentaenoic acid (EPA) daily as an adjunct to statin therapy in men with a relatively high baseline intake of omega-3s (Japanese patients) causes a significant reduction in the risk of major coronary heart disease events as well as stroke.[18, 19] Unlike the study by Brasky and colleagues, this trial could prove causation, demonstrating that fish oil reduces the risk of CV disease. It would be a shame if patients stopped taking their fish oil supplements, owing to an unwarranted fear regarding prostate cancer, and subsequently experienced a CV event or sudden death.

A possible indication that Brasky's paper is seriously flawed is that their data showed that the risk of prostate cancer decreased as the amount of pack-years of smoking increased.[1] Compared to non-smokers, there was a 3%, 13% (trend for reduction) and significant 19% lower risk for prostate cancer in those who smoked $\leq$ 12.5 pack-years, 12.5-25 pack-years and $\geq$ 25 pack-years, respectively (relative risk [RR] 0.97, 95% CI:0.84-1.11, p=0.63, RR 0.87, 95% CI:0.74-1.02, p=0.09, RR 0.81, 95% CI:0.69-0.95, p = 0.01). Moreover, those with diabetes had a 33% lower risk of developing prostate cancer compared to those who were not diabetic (RR 0.67, 95% CI:0.54-0.83, p=0.0003). However, a lower risk for prostate cancer in diabetics is, in fact, a well established phenomenon.[20]

In conclusion, the Brasky paper only demonstrates an association between plasma phospholipid omega-3s and subsequent prostate cancer risk; it cannot prove that omega-3 fatty acids (and particularly fish oil) cause prostate cancer. A more thorough overview of the pertinent literature suggests that increased omega-3 fatty acid consumption does not increase prostate cancer risk, and notably decreases prostate cancer mortality – and most certainly decreases risk for sudden death and CV events.

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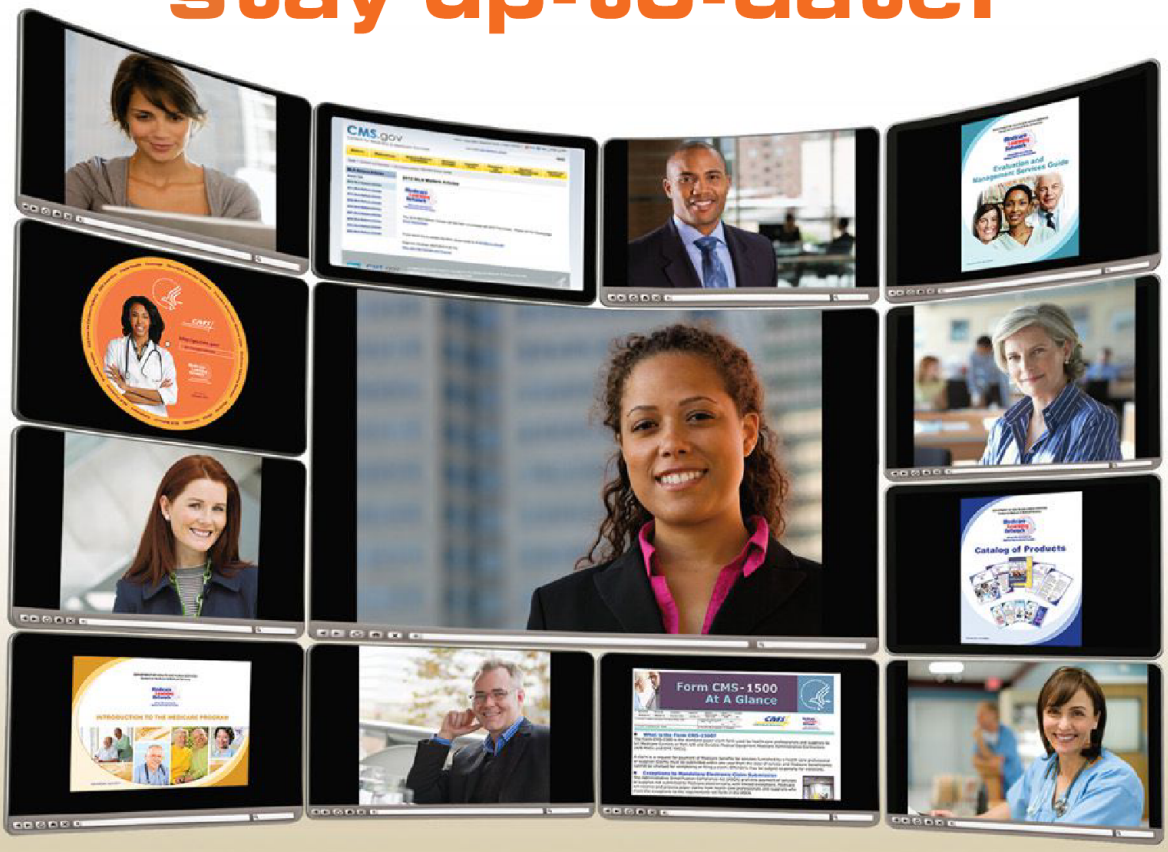
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# *In vitro veritas*: 90 years of Biochemistry at Saint Louis University

*by Joel C. Eissenberg, PhD & Enrico Di Cera, MD*

**The money generated from Dr. Doisy's patents on estrogens has been used for the benefit of our Department and the School of Medicine through a foundation that is today worth over $100 million. His professional accomplishments were honored with a 1944 Nobel Prize.**





Enrico Di Cera, MD, (left) is the Alice A. Doisy Professor and Chair, Edward A. Doisy Department of Biochemistry and Molecular Biology. Joel C. Eissenberg, PhD, (right) is Professor of Biochemistry and Molecular Biology and Associate Dean for Research. Both are at the Saint Louis University School of Medicine.
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The history of any academic department is written by each and every faculty, staff, and trainee. However, as the Edward A. Doisy Department of Biochemistry and Molecular Biology at Saint Louis University School of Medicine enters its 90th year, it is remarkable to note that the Department has only recently recruited its fourth chairman since it began. In this essay, we offer a brief history of the department through an account of these remarkable leaders and their contributions to biochemistry and to the growth of our department.

## 1924-1965

In 1919, Edward Doisy (See Figure 1), a young Harvard graduate, was hired by Dr. Philip Shaffer as Assistant Professor of Biological Chemistry at Washington University in St. Louis based solely on his affiliation with Otto Folin, Shaffer's former mentor. Four years later, Dean Hanau Loeb from Saint Louis University called Shaffer over the phone to offer Doisy a professorship, a position that Doisy would accept at Shaffer's insistence. In January 1924, the Department of Biochemistry was founded in the Medical School at Saint Louis University with Doisy as its first chair.

While still at Washington University, Dr. Doisy had started collaboration with Edgar Allen in the Anatomy Department that culminated in the landmark localization, extraction, and partial purification of an ovarian hormone. After moving to Saint Louis University, Doisy became convinced that isolation of the hormone would require processing of large quantities of biological specimens. He commissioned from a local metal concern a large scale continuous extractor for approximately $150. When it was finished, the bill was $750 – roughly the yearly salary of a junior professor in those days. When Doisy took the bill to Dean Loeb, he expected to be fired. The Dean did blink twice but approved the purchase. Dean Loeb died in 1927 and unfortunately could not witness the extraordinary returns on the investment that he had made by paying that bill. Between 1929 and 1936, Doisy discovered and isolated estron (1929), estriol (1931), and estradiol (1936), heralding the pharmacology of female sex hormones. Dr. Doisy and his junior colleague (and first PhD student) Dr. Philip Katzman, assigned the patents from these

discoveries to Saint Louis University in 1955 in return for the generosity of Dean Loeb. The money generated from Doisy's patents on estrogens has been used for the benefit of our Department and the School of Medicine through a foundation that is today worth over $100 million. Half of the buildings in the medical school bear the Doisy name, including the state-of-the-art Doisy Research Center, an $82 million modern construction that houses the entire Department of Biochemistry and Molecular Biology and several scientists from other basic science and clinical departments.



Figure 1: Edward Doisy, MD

The discovery of estrogens did not mark the zenith of Doisy's career. After three years of efforts using the large-scale continuous extractor that led to the isolation of estrone, Dr. Doisy succeeded in the extraction and synthesis of vitamin K from alfalfa and putrefied fish meal in 1939. When the Nobel Committee resumed its activities in 1944, after a hiatus of five years due to World War II, the 1943 Nobel Prize in Physiology or Medicine was shared by Doisy and Henryk Dam for the synthesis and discovery of vitamin K, respectively.

Dr. Doisy's commitment to the growth and development of the Department he founded was met with challenges, of course, and perhaps none as great as the Great Depression that gripped the country in the early and mid-thirties. Dr. Harold Katzman, one of Dr. Doisy's early faculty appointments, recalled that during this difficult time, he was summoned to Dr. Doisy's office and told that there were no funds to pay faculty salaries. When asked (several decades later) how he reacted, Dr. Katzman responded: "I felt lucky. At least I had a job."

Dr. Doisy remained at Saint Louis University as chair of the Department of Biochemistry until his retirement in 1965. The Department of Biochemistry was renamed the Edward A. Doisy department in his honor in 1955.

Dr. Doisy died in 1986 at the age of 92. Doisy's extraordinary accomplishments as a scientist, educator, and member of the Saint Louis University community have shaped a legacy of excellence and dedication that continues to inspire to the present day.

## 1965-1982

Robert E. Olson, MD, PhD (See Figure 2), succeeded Dr. Doisy as chair of the Biochemistry Department in 1965. This represented a homecoming of sorts for Dr. Olson, as he received his PhD training in the Biochemistry Department from 1939 to 1944. He returned to his alma mater having achieved national prominence as a leader in clinical nutrition research at the University of Pittsburgh. For this research, he received the McCollum Prize from the American Society of Nutrition. In his seventeen years as chairman at Saint Louis University, Dr. Olson maintained a vigorous research program that was continuously funded by multiple NIH research grants. In addition to holding leadership positions in the Biochemistry and Nutrition Societies and serving as editor to the American Journal of Nutrition, he served (1967-77) as Director of the Anemia and Malnutrition Center in Chiang Mai University in Thailand. He obtained a multi-million dollar grant to build the Center to study protein-calorie malnutrition in northern Thai children and recruited a clinical faculty contingent to serve on its staff.

Dr. Olson also championed clinical nutrition as an important part of physician training. He initiated the AOA Medical Student Research Forum for SLU medical students to achieve local and national recognition for their research. He also initiated the student-sponsored Wendell Griffith Lectureship in the

department, and the Wendell Griffith Book Award for graduating medical students.

Dr. Olson presided over the expansion of the Department to 18 faculty members, national recruitments to fill these positions, and successful efforts to attract national funding to support their research. Also of note is that Dr. Olson hired the first female faculty in the Department, Drs. Anna Marie Weber and Claudette Klein. He renovated a great deal of old space formerly housing the Chemistry and Biology Departments in the Medical School Building and transformed them into modern and well-equipped laboratories. He also was involved in the design of the state-of-the-art laboratories in the Doisy Research Wing of the Medical School building occupied by the Biochemistry Department.



Figure 2: Robert E. Olson, MD

Dr. Olson inherited a Biochemistry training grant for graduate students and postdoctoral fellows when he succeeded Dr. Doisy as chairman. When the NIH shifted its support to multidisciplinary training, he and one of his faculty appointees, Dr. William Longmore (as principle investigator), obtained a pulmonology training grant for graduate students, medical students, and postdoctoral fellows from the National Heart and Lung Institute. That grant supported translational research with members of the Biochemistry Department and clinicians from the Pulmonary Division of Internal Medicine.

Dr. Olson grasped the significance of the molecular biology revolution, and recruited the first molecular biologists to the department at a time in the sixties when they were in such great demand that they were difficult to find and land. He promoted the establishment of a separate training program in Cellular and Molecular Biology at the School of Medicine, which was supported for over two decades by NIH training grants. Most of the departmental faculty taught courses in the CMB program and many CMB students received their PhDs under the direction of Biochemistry Department faculty.

An anecdotal story illustrates Dr. Olson's mission-oriented approach to problem-solving: Once, Dr. Olson wanted to enter one of his laboratories in the medical school but the door was locked and he did not have the key to it. He called security and an officer showed up with a large ring of keys. However, the officer found that none of them opened the door. When the officer reported this to him, Dr. Olson demanded that he shoot the lock on the door to open it. Instead, the officer went back to his office and found the key to open the door.

Dr. Olson is remembered as a charismatic leader and an excellent educator. The causes he championed were for the good of the research and teaching mission of his Department and its members. In 1982, Dr. Olson was recruited to the University of Pittsburgh. He died on August 11, 2011, in Boston, Massachusetts, at the age of 92. Dr. William Longmore served as acting chair of the department for 18 months after Dr. Olson's departure until Dr. Sly was recruited as the next permanent chair.

## 1984-2010

William S. Sly, MD, (See Figure 3), succeeded Dr. Olson as chair of Biochemistry in 1984. Like Dr. Olson, Dr. Sly was a Saint Louis University graduate, receiving both his bachelor's and medical degree at the University. Since Dr. Sly had started his independent career as a lambda bacteriophage geneticist, before moving into the genetics, biochemistry, and cell biology of human inherited disease, he brought a first-hand appreciation of the role of both basic biomedical research and translational research to his plans for the Department.

Dr. Sly arrived having already achieved international distinction from his work on lysosomal storage diseases. He identified and characterized the first patient with beta-glucuronidase deficiency, also known as mucopolysaccharidosis VII or "Sly Syndrome." For these groundbreaking studies, he was inducted into the National Academy of Sciences in 1989.

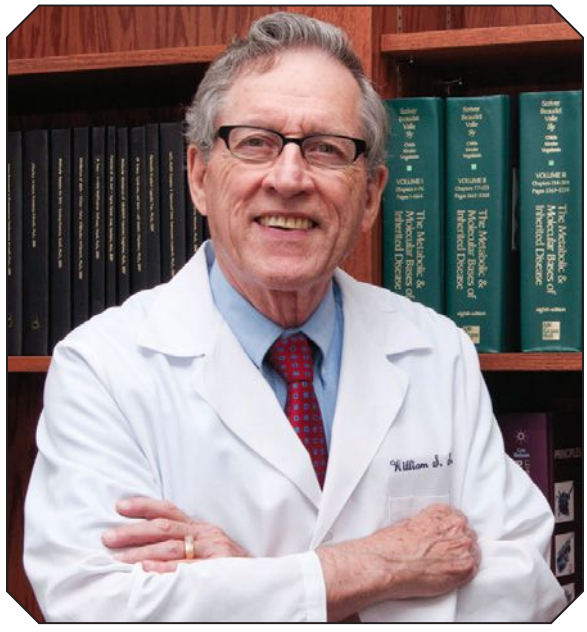


Figure 3: William S. Sly, MD

Very few physicians have described the first defining case of a genetic disease, but Dr. Sly has accomplished this twice in his career. In 1983, Dr. Sly showed that patients with a curious syndrome of renal tubular acidosis, osteopetrosis, and cerebral calcifications suffered from a deficiency in the enzyme carbonic anhydrase II. His laboratory at Saint Louis University School of Medicine cloned and characterized many members of the carbonic anhydrase gene family, and generated mouse deficiency models. In the course of this work, Dr. Sly and his colleagues solved the first X-ray crystallographic structure of a membrane-bound carbonic anhydrase, CA XII, an enzyme implicated in tumor progression. In 2009, Dr. Sly published the first data linking mutations in carbonic anhydrase IV to an autosomal dominant form of retinitis pigmentosa. Most recently, as an extension of his interest in carbonic anhydrase, Dr. Sly is collaborating with a local biotechnology company to develop an enzyme-based carbon capture device to reduce the atmospheric emission of carbon dioxide.

In the 1990s, Dr. Sly added a third research program in hemochromatosis, the disorder of iron overload. He was the first to demonstrate that functional loss of the human hemochromatosis gene product, HFE, causes hemochromatosis by generating the knockout mouse. Research directed by Dr. Sly provided the molecular link between HFE and iron metabolism by demonstrating that HFE protein associates with the transferrin receptor. He also led the project that determined the molecular basis for the most frequent HFE gene mutation causing hemochromatosis. As an extension of this work, Dr. Sly contributed to the discovery that functional loss of HFE led to inadequate production of the iron regulatory hormone hepcidin. The recognition of this relationship between hemochromatosis and hepcidin expression has helped to bring about a fundamental rethinking of how the body regulates iron absorption and distribution.

Dr. Sly's commitment to principles of fairness, justice, and integrity were most obviously manifested in the circumstances that brought to light a pitfall in the legal system's willingness to rush to judgment. In 1991, a St. Louis jury convicted Patricia Stallings of first-degree murder for poisoning her infant son with antifreeze, and sentenced her to life in prison without the possibility of parole. Upon seeing the purported evidence as described in a televised episode of "Unsolved Mysteries," Dr. Sly recognized that the blood test used by the commercial laboratory was incapable of excluding an inherited metabolic disorder. Despite skepticism from those who were otherwise convinced of the jury's conclusion, Dr. Sly ordered his Department's metabolic screening lab to conduct additional tests. The results pointed conclusively to a genetic disease, methylmalonate acidemia, which causes symptoms that overlap those of ethylene glycol poisoning. Dr. Sly wrote up these findings, which were forwarded to the prosecuting attorney in the case. His letter was crucial to the dismissal of the murder charges, and the innocent mother was released from incarceration.

Dr. Sly served for 20 years as co-editor for three successive editions of the definitive resource in clinical genetics, *The Molecular and Metabolic Bases of Inherited Diseases*. He has also served on the editorial boards of numerous

journals, as well as on the advisory boards of scientific societies, foundations, and companies.

Perhaps because of his history as a medical student at Saint Louis University, Dr. Sly took a strong interest in pre-clinical medical education, teaching many of the lectures in the first year Medical Biochemistry course himself. With the support of Dean William Stoneman, Dr. Sly founded the MD/PhD program at Saint Louis University School of Medicine.



Figure 4: Enrico Di Cera, MD

Upon his arrival, Dr. Sly implemented extensive renovations across the Department, which then occupied all of the first floor of Schwitalla and Doisy Halls. He initially made a major commitment to expand the hiring of molecular biologists initiated under Dr. Olson's chairmanship. During the first five years, he formalized this commitment by changing the department name to the Edward A. Doisy Department of Biochemistry and Molecular Biology. Other research initiatives of Dr. Sly's tenure as chair include the hiring of the first structural biologists in the Department and the installation of the first X-ray crystallography diffraction machine. He acquired a prototype Perkin-Elmer Polymerase Chain Reaction (PCR) machine for the Department in 1988, at the dawn of what he foresaw would become a PCR-driven revolution in molecular biology. Under Dr. Sly, the Department opened and maintained a metabolic screening laboratory using gas chromatography/mass spectrometry that continues to analyze pediatric specimens from all over the country for metabolic signatures of inborn errors of metabolism. In 2007, Dr. Sly oversaw the move of the Department from the home it had occupied in Schwitalla Hall to the newly built Doisy Research Center, where it remains today. It should also be mentioned that the Department and the School of Medicine enjoyed major improvements on the campus during the past 20 years under University President Father Lawrence Biondi, with the replacement of a block of city street that ran though campus by a pedestrian mall and the return of several surface parking lots to green space. Dr. Sly's motto throughout his administration was "What a great place to work!" He did his best to make this motto a reality for the faculty in the Department.

## 2010-present

Enrico Di Cera, MD (See Figure 4) assumed the chairmanship of the Edward A. Doisy Department of Biochemistry and Molecular Biology in January 2010. His arrival marked a return of this position to an internationally recognized leader in the biochemistry of coagulation. Dr. Di Cera's work has opened important new frontiers in the control of coagulation in thrombosis and uses X-ray crystallography in the structure-guided design of novel therapies. He has greatly expanded the departmental capability in structural biology with the acquisition of a new and more powerful X-ray diffraction facility and the establishment of a proteomics core facility for large-scale production of proteins for structural biochemistry. More recently, the Department has acquired a high-performance computing infrastructure for massive parallel throughput that benefits many areas of research within the Medical School, ranging from structural and computational biology to functional genomics and proteomics.

## Acknowledgments

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# Seed and Soil: A Conceptual Framework of Metastasis for Clinicians

*by Farhoud Faraji, BA & Joel C. Eissenberg, PhD*

**Decades of research have identified numerous elements critical to both the "seed" and "soil" components of metastasis, providing support for Paget's 1889 hypothesis. There is hope of improved outcomes with new and innovative therapies that target these specific pathways.**



Joel C. Eissenberg, PhD, (left) is Professor of Biochemistry and Molecular Biology and Associate Dean for Research at the Saint Louis University School of Medicine. Farhoud Faraji, BA, (right) is an MD/PhD student in the Department of Biochemistry and Molecular Biology and in the Saint Louis University/ National Institutes for Health Graduate Partnership Program, Laboratory of Cancer Biology and Genetics, Metastasis Susceptibility Section, Center for Cancer Research in Bethesda, Maryland.
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***"When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil."***
*~ Stephen Paget, 1889*

## Abstract

**Most mortality from cancer is secondary to metastasis. Metastasis refers both to the process by which tumor cells establish themselves at organs distinct from where they originated and to the life-threatening lesions themselves. Metastases are often resistant to conventional therapies, highlighting a key distinction between these progeny lesions and the primary tumor from which they arose. Here, we summarize recent advances in understanding and targeting primary tumors and the mechanisms and therapeutic challenges of metastasis.**

The English surgeon Stephen Paget proposed the "Seed and Soil" hypothesis to explain the mechanism of metastasis.[1] In it, he compared the dissemination of tumor cells to the distribution of seeds: each seed carries the potential for exuberant growth, but only the seeds that fall on compatible soil will realize that potential. Analogously, among the neoplastic cells released by a primary tumor, only the few that find their way to compatible organs will establish metastases. In addition, cells that escape the primary tumor face many barriers in the process of forming clinically relevant metastatic lesions.[2] The ability to target the metastatic process itself will transform cancer therapy. Here, we review the current state of our understanding of metastasis and persisting challenges uncovered by the latest research.

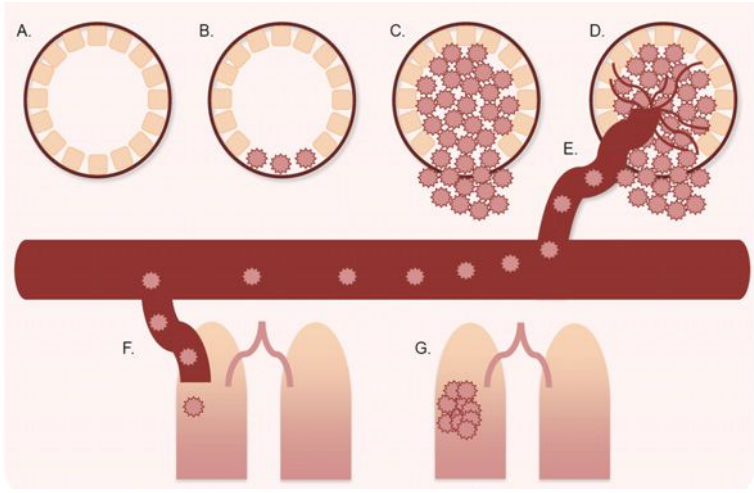
## The Medical Toll of Metastasis

A diagnosis of cancer leads to two critical questions: (1) has the tumor metastasized and (2) will the tumor metastasize? The gravity of these questions is underlined by the fact that the leading cause of cancer-related death is disseminated metastatic disease.[2] Yet most available therapies target primary tumor growth,

often showing little to no efficacy on metastatic lesions.[3]

The primary metric for enduring remission is survival at five years. However, this metric fails to capture patients who relapse beyond this point because disseminated tumor cells can recur many years after seemingly successful treatment. Disseminated tumor cells can exhibit a "dormant" state, remaining quiescent for years, even decades, in tissues foreign from their origin only to re-initiate growth when they acquire adaptive mutations or a more congenial environment within that tissue.[2,3] Understanding the mechanisms of dormancy and escape from dormancy may be key to preventing relapse.

***Figure 1***
***Steps of the Invasion-Metastasis Cascade***
Normal epithelium is depicted in yellow, tumor cells in red with jagged edges. (A) Normal epithelium with lumen (B) Carcinoma in situ: neoplastic transformation occurs with tumor cells confined within the epithelial basement membrane (C) Invasion: tumor cells fill epithelial lumen and begin to invade beyond the basement membrane and into the interstitial space (D) Neovascularization: vasculature is recruited to perfuse the expanding tumor (E) Intravasation: tumor cells invade into the vasculature and gain access to the systemic circulation; tumor cells travel to remote sites via circulation (F) Extravasation and metastatic seeding: tumor cells exit the vasculature and arrive at distant organ sites (G) Metastatic colonization: an extreme minority of seeded tumor cells adapt to the foreign environment of the distant site and begin to proliferate to form a clinically detectable metastatic lesion.




## The Cell Biology of Metastasis

Metastasis involves tumor cell-intrinsic behaviors and systemic factors not directly related to the tumor cells, known as host-derived factors. Tumor cell-intrinsic traits include aberrant motility, invasiveness, and cellular phenotypes associated with cell survival. Host-derived factors can include endothelial cells, platelets, macrophages, regulatory T-lymphocytes, fibroblasts and bone marrow-derived cells, and secreted factors not directly derived from tumor cells.[2]

In order to achieve a clinically relevant metastatic lesion, tumor cells undergo a multi-step process and often co-opt non-neoplastic cells. These steps are collectively termed the 'invasion-metastasis cascade' and include (1) tumor outgrowth beyond the basement membrane into the peripheral extracellular matrix, (2) recruitment of vasculature to sustain primary tumor growth, (3) invasion into this newly formed vasculature, (4) survival in the blood or lymphatic circulation, (5) arrest at the target organ, and (6) adaptation to thrive within this foreign tissue, termed metastatic colonization (Figure 1).[2] Moreover, mutations resulting in neoplastic transformation and genomic instability often result in expression of tumor cell-specific antigens, which can make these cells immunogenic.[4] As a result, while undergoing the invasion-metastasis cascade, metastatic cells must also evade the host immune system.[5]

### *Detachment from Primary Tumor and Traversing the Extracellular Matrix*

The first barrier to neoplastic cell dispersal is the surrounding extracellular matrix (ECM), including the basement membrane that compartmentalizes epithelial tissue. Successful neoplastic cells acquire the ability to survive detached from their substrate and secrete enzymes that dissolve the ECM, promoting dispersal from the initiating tumor. In addition to its role as a physical support for tissues and organs, ECM is also a storage site for growth factors. Thus, dissolution of the matrix can release proliferation-stimulating proteins locally in the tumor microenvironment. This release is facilitated by acquisition of a cellular phenotypic plasticity resulting from a de-differentiated state. Carcinomas, which are tumors of epithelial origin, undergo genetic reprogramming known as epithelial-to-mesenchymal transition (EMT), which is thought to endow them with motility, invasiveness, and matrix-dissolving properties that enhance their metastatic capability.[2,6] Although EMT has been consistently reported in the laboratory, observations of epithelial morphology of both primary tumors and metastatic lesions in patients have cast doubt on the relevance of EMT in human disease.[7]

Recent reports, however, substantiate the importance of EMT for dissemination, invasion, and arrival at the secondary site.[8, 9, 10] Further, these studies reconcile clinical observations of the epithelial morphology of metastatic lesions with direct evidence for reversion of EMT by a mesenchymal-to-epithelial transition. Evidence from a mouse model suggests that, although EMT is required to enable dissemination, upon arrival to the secondary sites tumor cells that had undergone EMT must revert to an epithelial state in order to proliferate and form full-blown metastatic lesions.

### *Entry Into Circulation*

For seeds, dispersal requires wind, water, or the digestive tracts of animals. For cells, the highways of dispersal are the lymphatic and blood circulation. Upon reaching a particular size, a tumor must recruit its own vasculature to sustain itself.[2, 6] Tumor-associated vasculature tends to be tortuous, dilated, and contains dysfunctional pericytes. These changes may reduce barriers to tumor cell access to the vasculature, a process called intravasation.[6] While metastatic cells can disperse through either the lymphatic or hematogenous circulation, the blood appears to be the preferred route for most metastases. That said, sentinel node status is informative for clinical staging and management of some cancers, including melanoma, breast cancer, and prostate cancer.

### *Survival in Circulation*

The circulatory system is a hostile environment for cells derived from solid tumors. Once in the circulation, pre-metastatic cells must acquire resistance to anoikis, a type of programmed cell death that results from loss of attachment to the ECM.[6] The cell membranes of invading cells, unlike blood cells, are not structured to withstand the shear forces of narrow vessels. Tumor cells may bind to platelets to shield themselves from shear forces and immune cells encountered in the blood stream.[11] The narrowest vessels, the capillaries, have internal diameters smaller than the diameter of most pre-metastatic cells, thus sieving many pre-metastatic cells from circulation. Once so arrested, tumor cells can either grow into metastatic lesions within the vascular lumen or invade organ parenchyma prior to forming a metastasis.

## Exit From Circulation

Pre-metastatic cells that survive the rigors of circulation must exit by once again pushing their way out through the vessel walls. This process is the reverse of intravasation, and is thus called "extravasation." While the most common sites for metastases are the lungs, bones, and liver, tumors with different tissue origins differ in their preferred sites of metastasis (See Table 1). The sites for extravasation may be dictated by 'passive tropism,' with exit simply being the nearest point to the site of intravasation that capillary sieving occurs (for example, the liver for colon cancer cells). Absence of closely apposed mural cells on the vessel walls supplying bone marrow renders them more vulnerable to pre-metastatic cell seeding. In some cases, however, tropism of pre-metastatic cells may reflect a pre-adapted state for certain organs or tissues, including the expression of surface proteins, such as growth factor receptors or cell adhesion molecules, with special affinity for those environments. Evidence suggests that circulating tumor cells are disseminated to a wide variety of organs. However, whether these disseminated cells, the "seeds," form clinically relevant metastases depends on their ability to thrive within the "soil," microenvironmental tissue conditions of these organs.[2]

***Table 1***
***Most Common Sites of Metastasis by Tumor***

| Cancer type | Main sites of metastasis |
|---|---|
| Breast | Lungs, liver, bones |
| Colon | Liver, peritoneum, lungs |
| Kidney | Lungs, liver, bones |
| Lungs | Adrenal gland, liver, lungs |
| Melanoma | Lungs, skin/muscle, liver |
| Ovary | Peritoneum, liver, lungs |
| Pancreas | Liver, lungs, peritoneum |
| Prostate | Bones, lungs, liver |
| Rectum | Liver, lungs, adrenal gland |
| Stomach | Liver, peritoneum, lungs |
| Thyroid | Lungs, liver, bones |
| Uterus | Liver, lungs, peritoneum |

*Source: http://www.cancer.gov/cancertopics/factsheet/sites-types/metastatic*

### *Adaptation of Metastatic Cells to Ectopic Sites*

Many environments are hostile to seed dispersal: large bodies of water, rocky or sandy soil, and sites of excessive shade or sun exposure. Likewise, most pre-metastatic cells are poorly adapted to the environment they confront upon extravasation. Indeed, successful colonization of the metastatic site is believed to be the rate-limiting step in metastasis.[2] Like seeds that initially

find themselves in hostile soil and remain dormant until conditions favor germination, pre-metastatic cells may remain quiescent or divide only slowly for years, and at a proliferation rate that may be balanced by significant cell death. For a micrometastasis to grow beyond a diameter of 1-2 mm requires the recruitment of a microvasculature to supply nutrients to the interior of the nascent tumor, a process called 'neoangiogenesis.'[6] Moreover, it appears that tumor-associated endothelial cells are distinct from normal endothelial cells, with distinct programs that make tumor-associated endothelia targets for novel therapeutic strategies.[12] Additional considerations may include: (1) the ability of tumor cells at the primary site to condition the secondary site's pre-metastatic niche congenial to tumor growth[13] and (2) acquisition of additional mutations by the pre-metastatic cells to promote adaptation to the foreign environment of the secondary site.[14]

## Models for Cancer Metastasis

The steps of the invasion-metastasis cascade outlined above highlight the barriers to metastasis and behaviors tumor cells must acquire to successfully metastasize. However, they provide little insight into the genetic and molecular determinants that enable a tumor cell to disseminate and colonize secondary sites. Several models have been proposed to provide a unifying framework for the molecular genetic basis of the invasion-metastasis cascade. Each model has particular strengths and weaknesses in explaining aspects of the invasion-metastasis cascade and most are not mutually exclusive views into the mechanics of metastasis. Here, we focus on two complementary models that explain most observations on metastasis (See Figure 2).

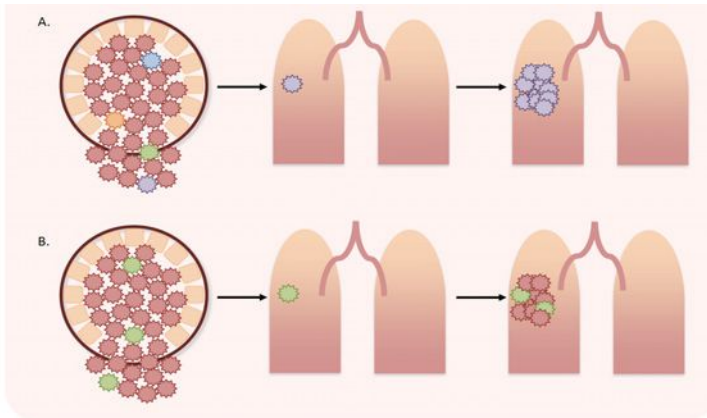
### *Clonal Selection Model*

This most widely accepted model for metastasis posits that neoplastic cells acquire metastatic capabilities through mutation and selection of the fittest clones. This hypothesis is based on the genetic instability inherent to tumor cells, which allows individual cells that acquire mutations to diverge from the parental cell followed by selection for certain mutant cells at sites foreign to the primary tumor.[14] This model incorporates the notion that only a small subset of cells in the primary tumor ultimately acquires the necessary properties to become metastatic lesions. However, it cannot explain the observation that, in some cases, gene expression patterns within the primary tumor can predict metastatic and survival outcomes, since this small subpopulation of cells is unlikely to contribute measurably to the aggregate gene expression patterns of the whole tumor.[15, 16]

### *Cancer Stem Cell Model*

Stem cells normally replenish aged and wounded tissue. Cancer Stem Cells (CSCs) are thought to be progenitors of tumor cells with self-renewing properties that enable sustained tumor growth. In the CSC model of metastasis, CSCs are thought to be the cells that are capable of forming tumors at secondary sites because they are the only cells within a tumor that can proliferate indefinitely. The CSC model differs from the clonal selection model in that all tumors have a pre-existing subpopulation of intrinsically metastatically competent cells rather than metastatic cells arising by clonal evolution.[17] This model could account for observations of anaplastic tumors being more malignant and of cells in de-differentiated states that are thought to induce epithelial-to-mesenchymal transition, concepts gaining prominence in metastasis biology.[2, 18] However, this model fails to explain differences between mutational profiles and specific gene expression in primary tumors and matched metastases.[15]

***Figure 2***
***Models of Metastatic Progression***
Normal epithelium is depicted in yellow, tumor cells in red with jagged edges. (A) The clonal selection model: as the tumor progresses, tumor cells acquire mutations, some of which enhance metastatic capacity and only those tumor cells with favorable mutations (purple) metastasize. Genotypically distinct tumor cells are depicted in different colors. (B) The cancer stem cell model: the tumor is made of a minor subpopulation of cancer stem cells (green) that are the only cells within the tumor that can initiate new tumors, including metastases.



## The Molecular Genetics of Metastasis

Molecular genetic approaches to cancer over the past 35 years have uncovered two broad classes of genes that drive carcinogenesis: oncogenes and tumor suppressor genes. Oncogenes represent genes whose normal function is usually associated with cell survival and promotion of cell division. Abnormal amplification or hyperactivity of oncogenes contributes to the transformation of normal cells to neoplasms. Tumor suppressor genes, in contrast, normally act to prevent cell division and sensitize cells to signals for cell death and senescence. Their inactivation results in the loss of safeguards against uncontrolled cell proliferation. In human cells, few—if any—endogenous genes are capable of single-handedly transforming a cell. Both oncogene-activating and tumor suppressor-inactivating mutations are typically required for carcinogenesis to occur.[19]

Complicating the mutational profile of tumors is the intrinsic genomic instability of tumors, which results in many more mutations than are required for tumorigenesis and metastatic progression. Mutations in genes that cause tumor initiation and progression are known as "driver" mutations. However, due to the high mutational propensity of tumor cells, many "passenger" genes having no effect on tumor progression are also mutated. Resolving which mutations are drivers and which are passengers will enhance our ability to utilize targeted therapeutics. Encouragingly, it may also be possible to target certain passenger genes, as they sometimes present vulnerabilities specific to cancer cells.[20]

While oncogene and tumor suppressor gene mutations are drivers for tumorigenesis, these mutations contribute little to a tumor cell's metastatic ability. New classes of metastasis-specific genes, termed metastasis suppressors and metastasis promoters, are emerging that often have little impact on primary tumor growth but significantly enhance invasive and metastatic properties of tumor cells.[21]

Recent research has uncovered a new class of "genes," known as noncoding RNAs (ncRNAs), that produce RNA products that do not code for protein but enhance or suppress the expression of protein-coding genes. Various short ncRNAs (microRNAs, or miRs) and long noncoding RNAs (lncRNAs) have been implicated in carcinogenesis and metastatic progression, some acting as inhibitors and others as promoters.[22, 23] The discovery of these new regulators presents new opportunities for novel drugs that either mimic or antagonize the activity of ncRNAs.[22] Indeed, inhibitors of microRNAs are in pre-clinical testing and molecules that can degrade messenger RNA are in early stages of clinical and pre-clinical testing.

## The Tumor Microenvironment

A metastatic lesion is the culmination of complex interactions between tumor-intrinsic behaviors and host-derived factors. While much research on tumor biology has focused on behavior of the tumor cell, over the past decade the critical role of the tumor microenvironment in tumor progression and metastasis has become apparent. The tumor microenvironment is comprised of non-neoplastic cells in the immediate vicinity of tumor cells and includes myoepithelial cells, endothelial cells, lymphocytes, myeloid cells, and fibroblasts, as well as non-cellular components such as the extracellular matrix and secreted factors. It is now clear that tumor cells actively interact with their microenvironment to enhance tumor cell invasiveness and immunoevasiveness and to prime distant sites for colonization.[2, 3] An early indication of this was an experiment showing that ECM extract from normal cells quelled the invasiveness of tumor cells while the ECM from a tumor made tumor cells more aggressive and invasive.[24]

The cell-mediated immune system continuously surveys cells for intracellular antigens. Tumors evade this surveillance by, for example, turning off the expression of co-receptors that allow lymphocytes to bind tumor cells, thereby allowing them to escape detection both at the primary site and systemically. Moreover, several cell types within the tumor microenvironment, including regulatory T cells and myeloid-derived suppressor cells, suppress immune cell responses against tumor cells.[5, 25]

Tumor cells may have interactions that reach beyond the immediate microenvironment, sending systemic signals to prime the secondary environment and fertilize its metaphorical soil prior to their arrival. In experiments that established the concept of the "premetastatic niche," it was shown that tumor cells secrete exosomes—lipid-bound particles containing pro-metastatic proteins and RNA—into the circulation that are taken up by bone marrow derived cells (BMDC). These exosomes were shown to enhance BMDC arrival in the lung and remodeling of the lung tissue architecture to render it amenable for tumor cell colonization.[13, 26]

## Therapeutic Outlook

Depending on the type of cancer, its gene expression profile, and the characteristics of the patient, metastatic cancers can be treated with local therapy (e.g., surgery or radiotherapy), systemic therapy (e.g., chemotherapy, hormone therapy), or both.[2] The standard armory of non-surgical anti-tumor therapies—radiation and drugs—targets rapidly proliferating cells. While these approaches do lead to primary tumor regression, slower-dividing

cells within the tumor, such as cancer stem cells, may survive the treatment period and seed new tumors at the primary and metastatic sites. Similarly, occult metastases that are still dormant would escape therapies targeted to dividing cells. This evasion may help explain why progress in treating metastases has been incremental.[3]

The good news is that the metastatic process is very inefficient so, presumably, detection and removal of the primary tumor prior to metastatic colonization may lead to complete remission. Despite this, examples exist, such as lung and pancreatic adenocarcinomas, in which primary tumors metastasize before the primary tumor is detectable with current technology. The bad news is that successful metastatic cells may differ genetically from the primary tumor from which they are derived, so targeted therapy for the primary tumor may not be effective against its metastases.[14, 19] In light of this difference, the ideal therapeutic would induce regression of established macroscopic metastases.

***Table 2***
***Molecular Markers and Indicated Therapeutics***

| Molecular marker | Clinical setting | Treatment indicated |
|---|---|---|
| BCR-ABL translocation | Chronic myeloid leukemia; acute lymphoblastic leukemia | Imatinib, dasatinib, nilotinib |
| BCR-ABL translocation, imatinib-resistant | Chronic myeloid leukemia | Dasatinib, nilotinib |
| PML-RAR translocation | Acute promyelocytic leukemia | All trans retinoic acid |
| KIT mutation | Gastrointestinal tumor | Imatinib |
| HER2 amplification | Breast cancer; gastric cancer | Trastuzumab, lapatinib, pertuzumab |
| Estrogen or progesterone receptor-dependent | Breast cancer | Multiple hormone-based therapies (for example, aromatase inhibitors, ER/PR antagonists) |
| EGFR mutation | Non-small-cell lung cancer | Erlotinib, gefitinib |
| ALK fusion gene | Non-small-cell lung cancer | Crizotinib |
| BRAF mutation | Melanoma | Vemurafenib |
| BRCA1/2 mutation | Breast, ovarian cancer | PARP inhibitors (e.g. olaparib) |
| CTLA | Melanoma | Ipilimumab |
| MET and VEGFR2 | Medullary thyroid cancer | Cabozantinib |
| VEGFR | Colon, lung, breast, kidney, brain cancer | Bevacizumab |
| VEGFR, PDGFR, MAP-kinase pathway | Kidney, liver cancer | Sorafenib |
| VEGFR, PDGFR, c-KIT | Kidney, soft tissue sarcoma | Pazopanib |
| Non-specific Tyrosine Kinase inhibitor | Kidney cancer, imatinib-resistant gastrointestinal stromal tumor | Sunitinib |
| RANK/RANKL | Breast, prostate cancer | Bisphosphonates, denosumab |

*Source: Adapted from Collisson et al., 2012*
*Also see: http://www.cancer.gove/cancertopics/factsheet/therapy/targeted*

## *Advances in Classification of Tumors*

Currently, two methods are used in the clinic to classify tumors for prognostication and selection of appropriate therapeutic strategies. The TNM staging method is used to predict the clinical behavior and potential prognosis of a tumor by assessing the size of the tumor ("T"), whether draining lymph nodes ("N") contain tumor cells, and whether any distant metastases ("M") are present. Although the TNM staging system provides clear prognosis and can indicate how aggressively a tumor should be treated in the higher stage cases (i.e., when many lymph nodes are involved or when distant metastases are detected), it is of little clinical value in cases where tumors show no signs of spread. Inevitably, some tumors showing no signs of nodal involvement or metastases will metastasize. Histological grading entails microscopic inspection of a biopsy by an experienced pathologist, provides insight into the morphological features of a tumor, and can inform therapeutic selection. Unfortunately, tumors with very similar microscopic features often have very different clinical outcomes and different oncogenic drivers.[27]

Enormous advances in speed and economy of DNA sequencing have resulted in systematic catalogs of tumors and corresponding normal tissue sequences. These catalogs are being assembled with the goal of identifying tumor-

associated mutations that enable oncogenic transformation and metastatic progression.[19] While the classification of tumors has for decades been based on histology, the application of genomics and transcription profiling has disclosed a more precise catalog of markers that is resulting in better therapeutic outcomes in some cases. In the context of breast cancer, mRNA expression patterns are starting to be used as prognostic tools in the clinic. Two such examples, MammaPrint and OncotypeDX, are currently being tested in clinical trials for node-negative breast cancer.[28] Ideally, the recent advances in sequence technology, coupled with our ever-expanding understanding of mechanisms of carcinogenesis and metastasis progression, will enable us to sequence tumor RNA and DNA, not only for prognostication, but to identify deranged molecular pathways which could then be targeted to shut down oncogenic and metastatic signaling cascades.[19]

### *Advances in Targeted Therapeutics*

Over the past decade, new classes of drugs have emerged that target molecules and pathways deranged in cancer. Some of these drugs have also shown efficacy against metastases. Table 2 summarizes targeted compounds that are either in current clinical trials or have been FDA approved for the treatment of specific tumors. Unfortunately, many of these drugs show transient effects as tumor cells mutate to acquire resistance, and most patients ultimately succumb to disease.[29] To overcome the acquisition of resistance by the tumor, the oncology field may adopt a paradigm similar to the anti-HIV therapeutic (HAART) strategy in which multiple independent pathways are simultaneously targeted. However, as the targeted therapeutics and mutational profiling in cancer are still in relative infancy, more must be learned about individual action of these drugs and their combination with classical therapeutics before the advent of trials combining multiple targeted drugs.

## Summary

Decades of research have identified numerous elements critical to both the "seed" and "soil" components of metastasis, providing support for Paget's 1889 hypothesis. As a result, the promise of new generations of drugs capable of disrupting both the seed and soil of metastatic progression are now within reach and, with them, the hope of improved outcomes with therapies that target these specific pathways.

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## Disclosure

None reported.

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SAINT LOUIS UNIVERSITY

# What Fruit Flies Can Tell Us About Human Birth Defects

*by Dale Dorsett, PhD*

**Fruit flies can provide relatively rapid and inexpensive methods to understand the molecular basis diseases and to develop potential therapies, particularly for rare conditions for which standard methods for drug development are not economically feasible.**



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## Abstract

**Many times, when a human genetic disease is mapped to mutations in a specific gene, little is known about the biological functions of the affected gene. Development of new therapeutic methods is facilitated by understanding the gene's biological roles. Such information can often be obtained in animal models, such as the fruit fly. Here we describe how understanding a gene's function in fruit flies has illuminated the etiology of Cornelia de Lange syndrome.**

## Introduction: Cornelia de Lange Syndrome

A few years ago, on a sweltering summer day in a park not far from Saint Louis, I met a 15-year-old boy and his mother. He only came up to his mother's waist. As I gazed down at his shining face, the features characteristic of Cornelia de Lange Syndrome (CdLS), a rare genetic disorder, were obvious even to me, trained as a fruit fly, not a human, dysmorphologist. Talking with his mother, I was surprised to learn that he had actually just been diagnosed only the week before by his aunt, who had read about CdLS online. The boy, with verbal skills that were unusually good for someone with this syndrome, was quite excited to explain why he was different. Although CdLS can be easily suspected based on highly characteristic facial features, including arched eyebrows, thin lips, and long philtrum, there's more to it. Individuals with this syndrome suffer a raft of more serious problems, including intellectual impairment, autism, slow growth, and limb and multiple organ abnormalities (See Table 1).[1]

It is not always recognized initially by physicians or other caretakers. In fact, it is not uncommon, particularly in more rural areas, for CdLS to go undiagnosed, as it was in this 15-year-old. Cornelia de Lange first described this condition, which is also called Brachmann de Lange Syndrome, in the 1930s based on two unrelated pediatric patients she saw in Amsterdam.[2] Today, a CdLS-likely diagnosis is made relatively easily by a physician who has seen a few cases and recognizes the pattern of abnormalities. Early diagnosis makes a difference. It can lead to substantial improvement in management, as many of the diverse health risks can be anticipated.[1]

Feeding is a very common problem. On the summer day I met this patient, I also met many caring family members of other patients, including a grandfather who had used

*Table 1*
*Common features of Cornelia de Lange Syndrome*

| Feature | Percentage of individuals affected[a] |
|---|---|
| **Development and behavior** | |
| Growth retardation | 100 |
| Intellectual disability | mean IQ 53, range <30 to 102 |
| Autism spectrum disorder | 65 |
| Speech disorders | + |
| Self injurious behavior | 70 |
| Physical aggression | 40 |
| **Facies** | |
| Microcephaly | 93 |
| Low posterior hairline | 92 |
| Bushy eyebrows, synophrys | 98 |
| Ocular abnormalities (ptosis, myopia, nystagmus) | 57 |
| Long curly eyelashes | 99 |
| Depressed, wide nasal bridge | 83 |
| Anteverted nares | 85 |
| Long philtrum, thin upper, downturned mouth | 94 |
| High arched palate | 86 |
| Widely spaced teeth, late eruption | 86 |
| Micrognathia | 84 |
| **Skin** | |
| Hirsutism | 78 |
| Cutis marmorata | 56 |
| Hypoplastic nipples, navel | 50 |
| **Extremities** | |
| Micromelia | 93 |
| Reduction defects, oligodactyly | 27 |
| Clinodactyly (5th finger) | 74 |
| Simian crease | 51 |
| Proximally placed thumbs | 72 |
| Elbow flexion contractures | 64 |
| Syndactyly (toes 2 and 3) | 86 |
| **Genitalia** | |
| Hypoplasia | 57 |
| Undescended testes | 73 |
| Hypospadias | 33 |
| **Gastrointestinal** | |
| GE reflux | + |
| Gut duplication, malrotation | + |
| Volvulus | + |
| **Other** | |
| Hearing loss | 60 |
| Structural heart defects | 33 |
| Kidney, urinary tract defects | 36 |
| Thrombocytopenia | + |

[a]Data from references 21-25. [b]"+" indicates reported in multiple individuals.

techniques similar to those he used to handle young livestock on his farm to develop a diet that was palatable to his granddaughter. I also met a young mother who refused to accept being told by her pediatrician that poor mothering was responsible for the failure of her beautiful daughter to thrive, and who ferociously sought out other opinions until the correct diagnosis was made.

## Six Degrees of Separation: Making the Connection

You might wonder why a fruit fly molecular geneticist was attending a CdLS family picnic? There is a connection! The answer goes back to the mid-1990s, when our laboratory was investigating how genes are turned on and off during the development of a fruit fly called *Drosophila melanogaster*. This insect is a "model organism" that offers powerful genetic and molecular tools. It has long been a tenet of the *Drosophila* research community that for most biological functions, ranging from metabolism and endocrinology to learning and memory, the fruit fly is equivalent to a simple small model of a human, but with a more compact genome and wings. We were looking for genes that control limb development and discovered one that we named Nipped-B, based on the moth-eaten appearance of the mutant wings.[3] Nipped-B, it turned out, controls development of several tissues.

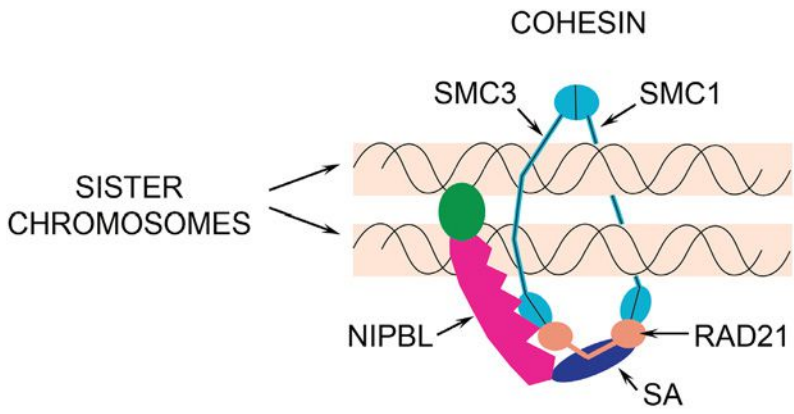



***Figure 1***
The NIPBL and cohesin protein complexes. The cohesin protein ring topologically encircles DNA, thereby holding replicated chromosomes together until cell division, to ensure proper chromosome segregation[20]. The cohesin complex has four subunits: Smc1, Smc3, Rad21, and SA. Smc1 and Smc3 have long arms, and Rad21 bridges the enzymatic head domains of Smc1 and Smc3. The cohesin ring is opened by NIPBL to snap it around chromosomes, and Rad21 is either removed or destroyed to reopen the ring and allow chromosomes to separate when a cell divides. As described in the article, cohesin and NIBPL bind to many genes on chromosomes and control their activities. Changes in expression of these genes are the underlying cause of the many physical and intellectual deficits in Cornelia de Lange syndrome.

It also soon became apparent, first from genetic studies with the equivalent genes in yeasts, that Nipped-B is also important in ensuring that chromosomes are dealt out equally to the two daughter cells when a cell divides. Nipped-B protein helps a protein ring called cohesin snap like a bracelet around chromosomes and hold sister chromosomes together, so they can be separated and sent in opposite directions at the moment of division (See Figure 1). It actually doesn't take much Nipped-B or cohesin, less than 20% of normal, to ensure proper chromosome segregation. Even a small reduction on the order of 30% or less can dramatically alter growth and development. This is because many other genes that are controlled by Nipped-B and cohesin produce either too little or too much of their products when Nipped-B is reduced.

## Making the Human Connection

The connection to human development, which we were sure would happen sooner or later (we could see the same gene in the DNA sequence of the human genome), came earlier than expected. In 2004, I received separate phone calls from Ian Krantz at the Children's Hospital of Philadelphia and Tom Strachan at the University of Newcastle, who had both recently discovered that mutations in the human Nipped-B gene, which they named Nipped-B-Like (NIPBL), caused most cases of CdLS.[4, 5] Both were seeking any insights we might have into how NIPBL might be involved in the diverse deficits associated with CdLS. Since that time, Ian and others have found that mutations affecting portions of the cohesin ring can cause milder forms of CdLS, or a similar syndrome.[6-8] Most recently, mutations in a gene encoding an enzyme that chemically modifies the cohesin ring were also found to cause CdLS.[9]

Mapping the first CdLS gene was not for the faint of heart. The NIPBL mutations that cause CdLS are genetically dominant and it is extremely rare for the disorder to be inherited – virtually all cases are caused by sporadic mutations. As a consequence, the usual method of following family lineages could not be used. The key was that beginning in the 1970's, Laird Jackson of Drexel University, responding to some questions from some concerned CdLS mothers, began organizing CdLS family picnics in the US, and traveling around the world to meet other CdLS families. Laird had the foresight to collect blood samples from the CdLS children, parents, and siblings, so that a large number had been collected by the time the human genome sequence became available. This collection allowed linkage exclusion analysis to narrow things down to five regions that might harbor the critical gene. Coupled with some inspired guesswork, and a balanced *de novo* chromosomal translocation affecting one of the five suspect regions, this analysis led to NIPBL.

Identification of NIPBL led to the first CdLS Scientific Symposium in June 2004, held in Lincolnshire, Illinois, in conjunction of the biennial family meeting organized by the CdLS Foundation that had grown out of the picnics organized by Laird many years before. I was invited to talk about our work with fruit flies, which began my association with the CdLS Foundation, as a member of the Board of Directors from 2004 to 2010, and currently as Chair of their Research Council.

One of the responsibilities that I have enjoyed is meeting CdLS families at occasional family picnics along the I-70 corridor from western Illinois to eastern Kansas. It is gratifying to reassure parents that it is nothing they did wrong that caused their child's condition. They find it a relief to have the genetics and causes of CdLS explained to them, and also to learn that there are dedicated physicians and scientists who care about this rare condition, and are

working hard to improve the methods of diagnosis and treatment. They are excited to learn that members of the Clinical Advisory Board of the CdLS Foundation, who have diverse expertise, can be approached to address their many medical questions. They are also thrilled to learn that teams of scientists are exploring the mechanism of the disease in search for clues to treatments that could improve their children's lives.

So, why do we think there is hope for developing effective treatments for CdLS? The problems with growth and development begin *in utero*, and CdLS has been diagnosed by ultrasound (e.g., reference 10). It is not beyond imagining that in the near future, CdLS, like many other rare disorders, can be diagnosed early in pregnancy with a combination of ultrasound, DNA sequencing, and molecular markers. As a rare, non-inherited genetic disorder, however, it would not become routine to check for CdLS until a safe method that can detect many genetic problems with early development is available.

If *in utero* diagnoses can be made, it would then be feasible to think about very early therapeutic intervention that could ameliorate many of the physical deformities. I also believe that therapeutic intervention that begins within a few weeks of birth could be very helpful. Surgery can be used to correct the occasional severe congenital heart defects, which are a leading cause of early death.[11] We can even envision the possibility that we can improve growth and intellectual development.

Mental retardation, poor speech, and autism are major impediments that keep most individuals with CdLS reliant on constant care and from becoming independent. There is good reason to believe that brain development is highly plastic, and that early intervention may greatly improve intellectual development of children with CdLS. For instance, using a mouse model of Rett syndrome, a leading cause of mental retardation in girls, Adrian Bird's laboratory in Edinburgh showed that turning the affected gene back on even in young adults led to substantial improvements in learning, memory, and behavior.[12] Similarly, flies with Nipped-B and cohesin deficits show delays in axon pruning and problems with dendrite branching,[13] two key processes in neural development, which have the potential to be corrected later in development. That's the long-range hope.

## Research 'Flies' By

Where do we start, and what strategies might lead to therapeutic discoveries? First we need to know how NIPBL and cohesin control genes, what genes they control, and when they control them, in order delineate what is possible. Our laboratory has exploited the fruit fly to gain some of this knowledge. Using techniques that allow us to examine the entire genome, we mapped where the Nipped-B and cohesin proteins bind to chromosomes in multiple types of cells and tissues, and which genes produce too little or too much product when the amount of Nipped-B or cohesin is reduced. These studies have provided important clues.

We discovered that Nipped-B and cohesin bind selectively to hundreds of active genes that control growth and development, and that the products of many of these genes and the genes they control are often altered when there is too little Nipped-B or cohesion.[14-18] Strikingly, one of the key genes that binds Nipped-B and cohesin and whose output decreases when there is too little Nipped-B or cohesion, is *myc*, a key growth promoter in both flies and humans. The *myc* gene is perhaps best known for causing cancer when it is too active, leading to unchecked growth. In *Drosophila*, *myc* is called *diminutive*, because the first mutation, isolated back in the 1930's, only partially reduces gene function, giving rise to tiny flies.[19] It turns out that the zebrafish, mouse, and human *myc* genes are also down-regulated when the *NIPBL* activity is reduced, providing one potential explanation for why CdLS was once known as "Amsterdam dwarfism."

The overriding message of our *Drosophila* studies, and parallel work by other laboratories in cultured mammalian cells, zebrafish, and *NIPBL* mutant mice, is that NIPBL and cohesin directly control the activity of hundreds of genes important for growth and development.[20] Many of the physical defects and other medical problems that are apparent upon birth can be handled with existing medical procedures. The diversity of the effects on gene function argue, however, that we will likely need to increase the activity of the remaining good *NIPBL* gene if we are to improve future development. It is easier to control a river at its source than at the delta.

The reality is that drug companies would go out of business if they poured buckets of money into developing treatments for disorders that occur on the order of once per ten thousand births. Different strategies have to be developed for identifying and developing effective drugs for orphan diseases. A model that we are testing for CdLS is to use fruit flies to screen libraries of chemical compounds that have already been approved for human use for the ability to enhance expression of Nipped-B. The idea is that this is a rich source of bioactive compounds, and it is not nearly as expensive to repurpose a drug as it is to develop a new one.

In collaboration with the laboratory of Justin Fay at Washington University, we screened a library of FDA-

approved drugs for those that improve the growth of yeasts that have modest defects in their *NIPBL* and cohesin genes, and then tested the dozen or so that had the desired effect for their ability to improve some of the mutant phenotypes displayed by *Nipped-B* mutant flies. This analysis identified a few chemically-related compounds that were able to normalize the levels of *NIPBL* RNA in cell lines derived from individuals with CdLS. One of these compounds is used to treat other pediatric conditions. That's hopeful! We are now seeking funding to test these compounds in a mouse model of CdLS, and consulting with physicians, allied health professionals, and CdLS families to decide what biomarkers can be used to conduct a meaningful clinical study in CdLS patients.

## Conclusion

My take-home lesson is fruit flies and other non-vertebrate organisms can prove to be useful models for human maladies. They can provide relatively rapid and inexpensive methods, both to understanding the molecular basis of the disease and to developing potential therapies, particularly for rare conditions for which standard methods for drug development are not economically feasible.

## Acknowledgments

The author is grateful to the CdLS families for their willingness to share their experiences, the CdLS Foundation, and Ian Krantz, Matt Deardorff, Laird Jackson, and Antonio Musio for many illuminating discussions. Work in the Dorsett laboratory is supported by grants from the National Institutes of Health (R01 GM055683, P01 HD052860).

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## Disclsoure

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# The Two Faces of DNA Repair: Disease and Therapy

*by Alessandro Vindigni, PhD & Susana Gonzalo, PhD*

**A major breakthrough in the treatment of breast cancers with the poorest prognosis, BRCA1-deficient and triple-negative breast cancers, was the finding that these tumors are exquisitely sensitive to PARP inhibitors.**



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## Abstract

**Our genome is the blueprint for our bodies. A number of sophisticated mechanisms help protect our genome from life-threatening cellular mistakes and environmental insults. Much current research focuses on understanding these mechanisms, how they prevent disease, and whether they can be targeted for therapeutic purposes. Here, we review the main mechanisms maintaining genome integrity, how their malfunctioning results in disease, and the exciting progress toward targeting these mechanisms for cancer treatments.**

## Genome Instability

Maintaining the stability and the correct sequence composition of the three million bases that form our genome is critical for a correct transmission of genomic information. Unfortunately, our genome is under constant attack by agents that arise from either normal metabolism or exposures to natural or artificial products in the environment.[1] As many as $10^5$ lesions in DNA can occur per cell per day. DNA damage can result from side products of our normal metabolic activities, such as free radicals and reactive oxygen and nitrogen species, as well as from environmental factors such as UV radiation, X-rays, and chemical compounds.[2] Our cells have evolved elegant mechanisms to cope with all these threats.[3] Improper or inefficient repair of DNA damage causes mutations, abnormal chromosome structures, or loss of genetic information that could ultimately lead to a large number of human syndromes, including premature aging, various cancer predispositions, and genetic abnormalities.[2,3] A large body of evidence has also implicated alterations in nuclear architecture and chromosome structure (so-called "epigenetic changes") in genomic instability. Furthermore, defects in the structure of chromosome ends and in the integrity of the energy factories of our cells, the mitochondria, profoundly impact the stability of our genome. The degree of genomic instability caused by alterations in any of these mechanisms will determine whether the cell survives, undergoes a permanent growth arrest known as senescence, or dies.

## The DNA Damage Response

The cell has evolved a complex pathway, termed the DNA damage response, to sense, signal, and ultimately repair DNA lesions arising from endogenous or exogenous insults.[3] A variety of DNA repair mechanisms, with specificity towards different categories of DNA damage, have been identified. These include mechanisms devoted to repair single-stranded DNA lesions, such as those caused by UV light and certain chemicals, and mechanisms responsible for the repair of DNA double-strand breaks, such as those caused by X-rays and anti-tumor agents like cisplatin and mitomycin C. Homologous recombination (HR) and non-homologous end joining (NHEJ) are the two main pathways required to repair double-strand breaks. These two pathways have been extensively characterized due to the fact that these lesions are particularly dangerous to the cell.[4] While NHEJ is an error-prone mechanism for DNA double-strand break repair, HR repairs the damage with great fidelity by utilizing sister chromatids as templates for recombination (See Figures 1 and 2).

DNA damage response is a complex pathway that mobilizes and recruits a variety of nuclear proteins to sites of DNA damage. Activation of this pathway can halt cell-cycle progression until the damage is restored, or initiate mechanisms of growth arrest or cell death if the damage is beyond repair.[5] A growing list of factors has been clearly implicated in DNA damage response. These factors include sensors of the lesions that recruit and activate the ATM and ATR kinases at sites of damage. ATM is a master regulator that activates a variety of factors involved in DNA damage response and in cell cycle control. This process also facilitates changes in chromosome regions surrounding the break. These changes in turn permit the recruitment of the machinery required to repair DNA double-strand breaks. Two effectors have recently been in the spotlight due to their key roles in regulating the balance between the main pathways of double-strand break repair: the breast cancer type 1 protein (BRCA1), which promotes HR, and the tumor suppressor p53-binding protein 1 (53BP1), which facilitates NHEJ.[6,7]

## Diseases Associated With Genomic Instability

Almost invariably, mutations in DNA repair factors cause syndromes linked to genomic instability.[8] For example, loss of ATM function causes the genome instability syndrome *Ataxia-telangiectasia* (A-T). A-T is a devastating disorder characterized by progressive neuromotor dysfunction, thymic atrophy and immunodeficiency, predisposition to lymphoid malignancies, and high sensitivity to DNA damage-inducing agents such as X-rays. Three other diseases,

Figure 1
Top) Common endogenous and exogenous agents which generate different types of DNA lesions throughout the genome. Bottom) Mechanisms required for the repair of the different types of DNA lesions. Base-excision repair (BER) and nucleotide-excision repair (NER) are two mechanisms used to repair DNA single-strand breaks. HR, Homologous Recombination; NHEJ, non-homologous end-joining. 14-mer duplex DNA structure (pdb: 2M2C).

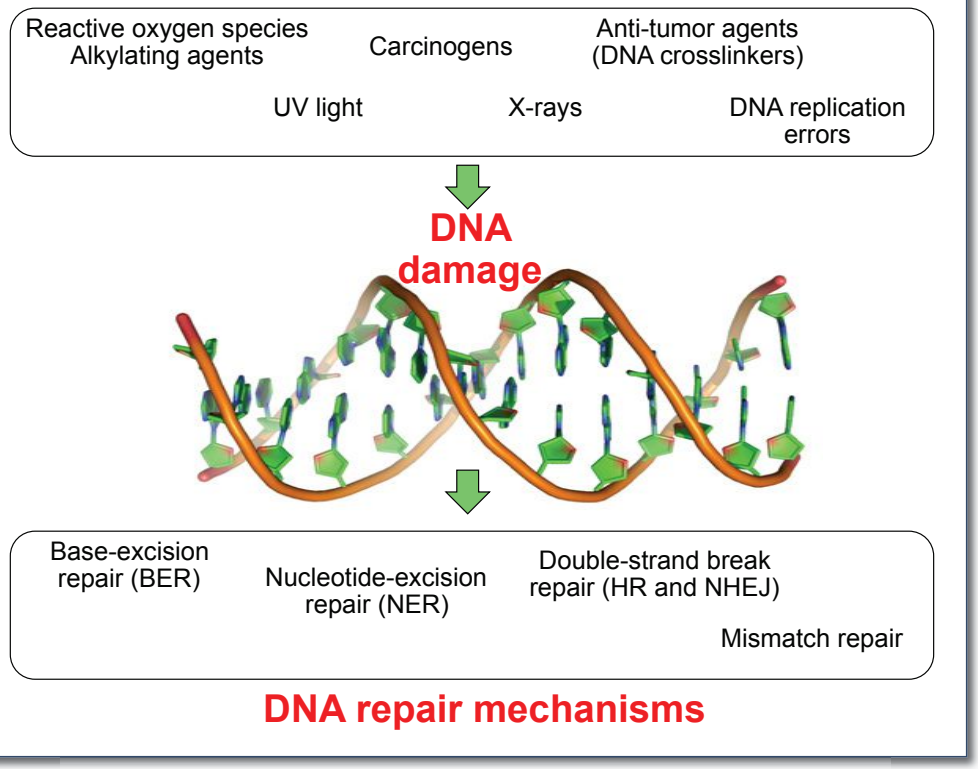
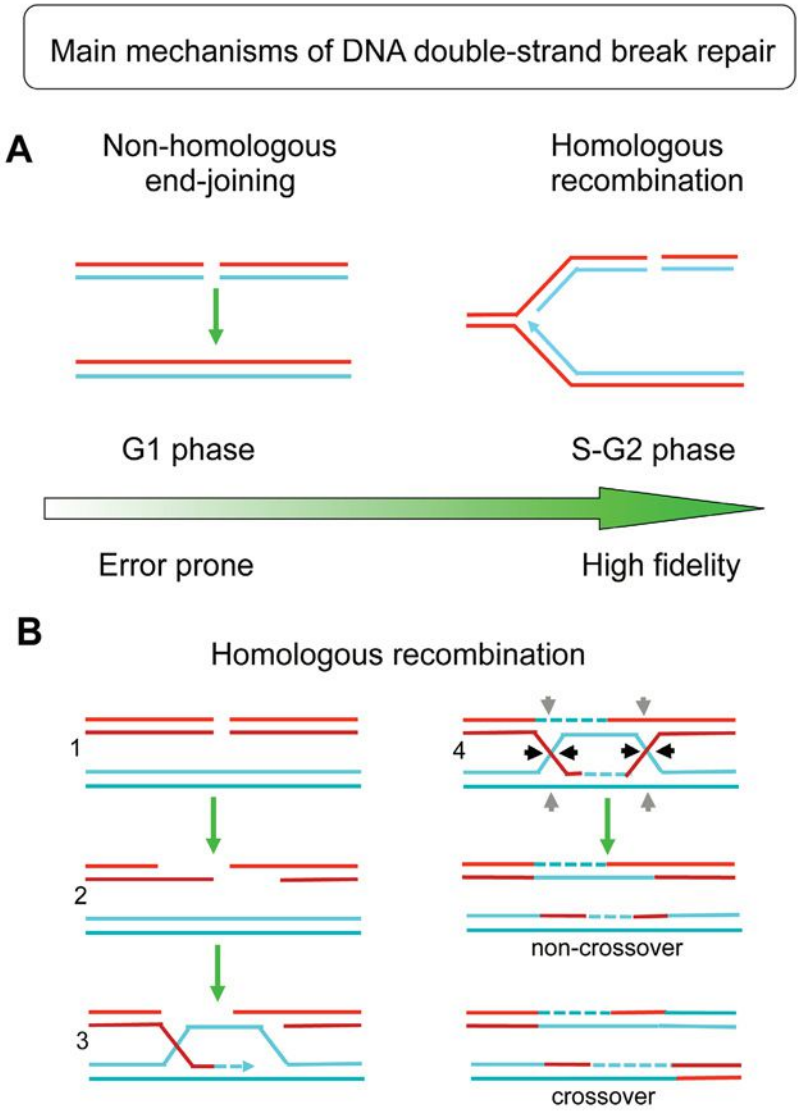


Figure 2
A) Main double-strand break repair pathways.
NHEJ directly seals the broken DNA ends and occurs primarily during the G1 phase of the cell cycle. HR is a high-fidelity repair mechanism that occurs primarily during the S and G2 phases of the cell cycle and requires the information contained in the sister chromatid. The figure on the right schematically shows a replication fork with a double-strand break on one of the strands.

B) Schematic model for the HR mechanism.
1) A double-strand break is present on the DNA template.
2) HR is initiated by resection of a double-strand break to provide 3' single-stranded DNA overhangs.
3) Strand invasion by these 3' single-stranded DNA overhangs into a homologous sequence is followed by DNA synthesis at the invading end.
4) The second double-strand break end is captured to form an intermediate with two Holliday junctions (HJs). The structure is resolved at the HJs in non-crossover or crossover products by specific HJ resolvases (black and grey arrow heads).




*Xeroderma pigmentosa* (XP), *Cockayne syndrome* (CS), and *Trichothiodystrophy*, are associated with defects in a specific single-strand break repair pathway.[9] In addition, alterations in other factors with key roles in DNA replication stress response are linked to genomic instability syndromes, such as *Fanconi anemia* and *Schimke immunoosseous dysplasia*.[10] RecQ helicases are an important family of DNA unwinding enzymes that play a key role in the maintenance of genome stability. Mutations in the genes of three human RecQ helicases are linked to defined genetic disorders associated with genomic instability, cancer predisposition, and features of premature aging; namely, *Bloom syndrome* (BLM gene mutations), *Werner syndrome* (WRN gene mutations), as well as *Rothmund–Thomson*, *Rapadilino*, and *Baller-Gerold syndromes* (all caused by mutation of RecQL4).[11]

In recent years, the generation of mouse models deficient in different DNA damage response pathways has provided important insight into the requirements for DNA repair pathways.[8] In many instances, mice lacking different DNA repair factors die during embryonic development, and conditionally deficient mouse models have been developed to test the effects later in life. Mouse models with DNA repair deficiencies often develop premature aging phenotypes and cancer. One of the best-characterized models is the histone H2AX deficient mouse. H2AX is a key coordinator of DNA damage response and mice that lack this protein exhibit radiation sensitivity, growth retardation, immunodeficiency, and male

infertility. These defects are associated with an impaired ability to assemble DNA repair factors at damaged sites.[12] Similarly, mice that lack 53BP1 show growth retardation, chromosomal instability, increased radiosensitivity, immunodeficiency, and cancer susceptibility.[13] Mice deficient in BRCA1 are embryonic lethal,[14] whereas conditional BRCA1-deficient mouse models have consistently increased risk of developing cancer, especially when combined with mutations in other tumor suppressor proteins such as p53.

## Genomic Instability and Cancer

Genomic instability has been most extensively studied in the context of cancer.[9] Hereditary or acquired mutations targeting DNA repair genes are often associated with aberrant DNA replication and increased genomic instability, leading to a neoplastic phenotype. In particular, mutations or chromosome rearrangements can contribute to the loss of tumor suppressor functions, or abnormal activation of oncogenes, which in turn result in uncontrolled cell growth, the hallmark of cancer. BRCA1 is one of the best examples illustrating a direct link between DNA repair activities and tumor suppression: women born with a mutation in BRCA1 have a high risk of developing breast and ovarian cancer. Like BRCA1, loss of other DNA repair factors increase the risk of tumorigenesis, as well as the sensitivity to DNA damaging strategies such as radiation or chemotherapy. In addition, deregulation of mechanisms of chromosome segregation leads to an abnormal dosage of chromosomes or aneuploidy, often triggering growth arrest or cell death, or providing the cells with a proliferative advantage.

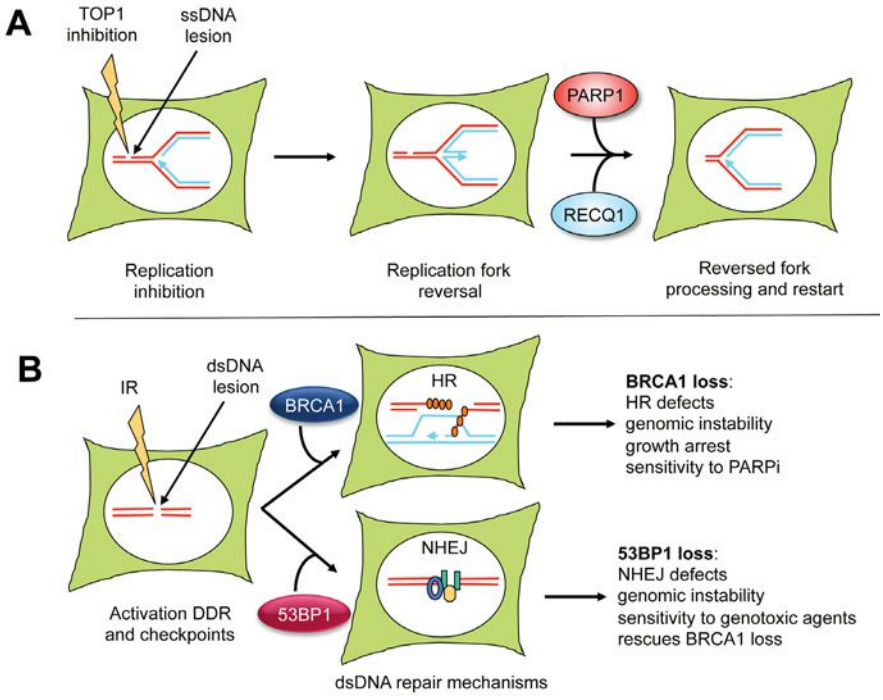
## Genomic Instability and Cancer Treatment

The presence of defects in specific DNA repair pathways in most cancers has been exploited for the design of commonly used chemotherapy and radiotherapy regimens in the attempt to selectively target actively proliferating cancer cells. For example, platinum salts (carboplatin or cisplatin) are frequently given in combination with taxane paclitaxel to patients with advanced ovarian cancer. Platinum salts cause DNA

Figure 3

A) Schematic model for the mechanism of replication fork reversal and restart upon TOP1 inhibition. The DNA replication fork is schematically shown in the white circle that represents the cell nucleus. TOP1 inhibitors trap TOP1 on the nicked DNA intermediate, thereby preventing repair of the ssDNA lesion, and causing the replication forks to reverse. RECQ1 is required to restart the replication forks reversed by TOP1 inhibition. PARP1 prevents premature restart of the reversed forks by inhibiting RECQ1 activity (for more details see 20).

B) Balance between DNA repair mechanisms of homologous recombination and non-homologous end-joining is important for genome stability. BRCA1 promotes HR and 53BP1 facilitates NHEJ. Loss of either BRCA1 or 53BP1 causes genomic instability and cancer predisposition, while loss of both ameliorates the phenotype. Recent studies showed that cancer cells deficient in BRCA1 lose 53BP1 to survive and resist therapy.



inter- and intrastrand crosslinks that are repaired by a combination of mechanisms, including HR. These agents are particularly effective in patients with ovarian cancer because these tumors are commonly characterized by defects in key HR genes.[15]

An alternative approach based on inhibitors that directly target DNA damage response at the level of cell cycle regulation or DNA repair mechanisms has recently emerged as a new paradigm in cancer therapy.[16] These inhibitors often enhance the effectiveness of radiotherapy and chemotherapy in cells, and are thus currently being tested in preclinical and clinical trials. Understanding the mechanism of action of these drugs is of high clinical relevance, and has allowed the identification of genetic defects in DNA metabolism pathways that can either confer resistance or sensitivity to certain chemotherapeutic agents. Knowing which DNA repair pathway is defective in a tumor will facilitate the design of the appropriate therapeutic regimen. However, inactivation of a specific DNA repair pathway is often compensated by the activation of an alternative pathway, which becomes essential for tumor cell survival. This dependence on an alternative mode of repair can be exploited therapeutically by "synthetic lethality" approaches. Synthetic lethality is a genetic concept that refers to the combined inactivation of two pathways to induce cell death when inactivation of each individual pathway is not effective.[17] These new approaches have shown efficacy and reduced toxicity in preclinical studies, and hold great promise for cancer treatment as long as the defective pathways in a specific tumor can be identified. Thus, it is envisioned that these synthetic lethality approaches will need to be complemented by the discovery of robust biomarkers that allow the stratification of patients based on the type of DNA repair defects, so that the proper combination therapy can be delivered to the specific patient. These types of discoveries will bring us closer to individualized medicine.

## New Frontiers for Cancer Treatment

Current research in our Department aims to understand the mechanisms of action of DNA replication and repair inhibitors with the ultimate goal of developing new drug combinations for cancer therapy. DNA topoisomerase I inhibitors, such as irinotecan and topotecan, could be regarded as the first generation of anticancer agents that target DNA replication. DNA topoisomerase I inhibitors are widely used for chemotherapy, but they are also highly toxic to many normal cell types. The mechanism of tumor response to DNA topoisomerase I inhibitors and the combination of DNA topoisomerase I inhibitors with other drugs for more effective tumor treatments is an area of vibrant investigation. Their cytotoxicity has been associated with their ability to generate single-strand breaks, which are eventually converted to double-strand breaks when the replication forks collide with the single-strand break.[18] Recent studies provided new insight into the molecular basis of DNA topoisomerase I inhibitor cytotoxicity by showing that clinically relevant doses of DNA topoisomerase I poisons trigger a process called "fork reversal" where the replication forks back up, thus preventing the collision of the fork with the single-strand break generated by the DNA topoisomerase I inhibitor (See Figure 3).[19] Following this discovery, our studies provided the first mechanistic insight into how this process occurs by showing that two DNA repair factors, the poly(ADP-ribose) polymerase 1 (PARP1) and the human RECQ1 helicase, play central roles in the accumulation and restart of reversed forks after DNA topoisomerase I inhibition.[20] These studies provide a new rationale for the development of novel targeted inhibitors to sensitize cancer cells to lower DNA topoisomerase I inhibitor dosages that are not toxic to normal cells.[20] Inducing fork reversal (DNA topoisomerase I inhibitors) and targeting the factors required for proper processing and restart of the reversed forks (PARP1 and RECQ1) should in principle synergize, thus increasing the DNA topoisomerase I inhibitor-sensitivity of cancer cells.

PARP inhibitors (olaparib and veliparib are the most extensively studied) have also received much attention as a promising therapeutic strategy for tumors that are deficient in the HR mechanism of DNA repair.[21] A major breakthrough in the treatment of breast cancers with the poorest prognosis, BRCA1-deficient and triple-negative breast cancers, was the finding that these tumors are exquisitely sensitive to PARP inhibitors.[22] Phase II studies with PARP inhibitors have shown a significant response rate in women carrying BRCA1 mutations with tolerable side effects.[23] Furthermore, PARP inhibitors potentiate the antitumor activity of current therapeutic strategies, such as genotoxic agents and ionizing radiation. A significant fraction of advanced BRCA1-related cancers

acquire resistance to PARP inhibitors. Landmark studies have demonstrated that loss of 53BP1 is "synthetically viable" with the loss of BRCA1 and induces resistance of BRCA1-deficient cells to PARP inhibitors.[24] Targeting the degradation of 53BP1 represents a new strategy for breast cancer therapy. Interestingly, our recent studies identified a mechanism contributing to the loss of 53BP1 in breast cancers. In particular, activation of the protease cathepsin L was found to contribute to 53BP1 degradation in breast cancer cells.[25] These findings provide a novel paradigm for the treatment of breast tumors that are resistant to PARP inhibitors due to the loss of 53BP1, such as the case of triple-negative and BRCA1 related cancers. In particular, inhibition of cathepsin L activity via treatment with vitamin D or specific cathepsin L inhibitors is expected to increase the levels of 53BP1, reduce proliferation, and restore the sensitivity of these tumors to PARP inhibitors and other DNA damaging strategies. These novel therapeutic strategies hold great promise for diagnosis, prognosis, and customization of breast cancer treatment.

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## Disclosure

None reported.

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SAINT LOUIS UNIVERSITY

# The Double Life of Antibiotics

*by Mee-Ngan F. Yap, PhD*

**Ultimately, it is through research and understanding of the microbes and the biological effects of each molecule at the metabolic level within the cell and within the microbial communities that will lead to new insights into antibiotic design.**

*"The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant."*
**~Alexander Fleming**



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## Abstract

**Antibiotic resistance is a persistent health care problem worldwide. Evidence for the negative consequences of subtherapeutic feeding in livestock production has been mounting while the antibiotic pipeline is drying up. In recent years, there has been a paradigm shift in our perception of antibiotics. Apart from its roles in self-defense, antibiotics also serve as inter-microbial signaling molecules, regulators of gene expression, microbial food sources, and as mediators of host immune response.**

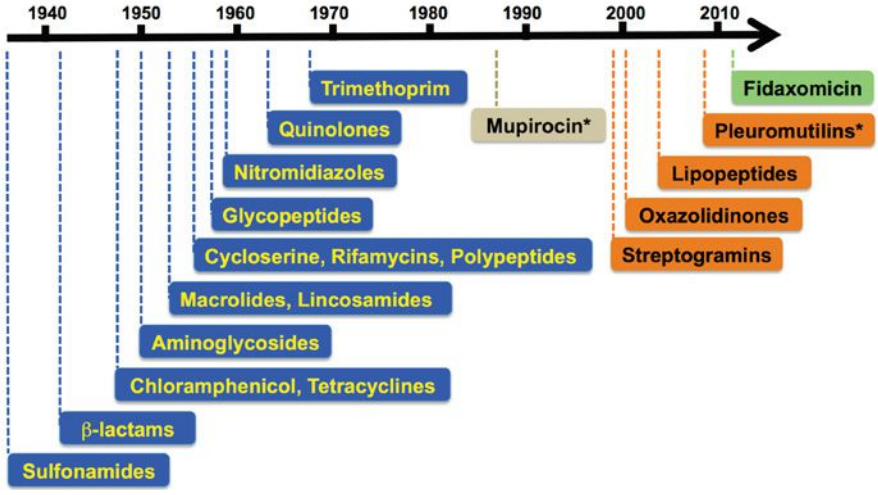
## The Growing Threat of Antibiotic Resistance

In 1945, the Scottish bacteriologist Alexander Fleming, who received the Nobel Prize for the discovery of penicillin, delivered the above cautionary statement in his Nobel lecture. His prophecy has since been fulfilled. Following the development of penicillin and sulfonamide (by the 1939 Nobel Laureate Gerhard Domagk), the serendipitous discoveries of antibiotics in the 1940s had inspired intense research into new human therapeutics. Fourteen classes of antibiotics representing six distinct mechanisms of action were introduced to clinical and veterinary uses before 1970 (See Figure 1).[1] They became the miracle drugs of the twentieth century and enabled common life-threatening infections to be treated for the first time. Yet after decades of extensive use (misuse, overuse, and habitual use), the medical community is facing an unprecedented challenge in combating antibiotic resistance. At the same time, bottlenecks have slowed drug discovery and development.

Every year at least two million people fall ill to hospital-acquired infections and approximately 100,000 of the cases are fatal, the majority due to resistant bacterial and fungal strains. The empty pipeline for antibiotics and the rapid erosion of drug efficacy pose

serious health risks in modern medicine. As antibiotics become ineffective, cases of hospital-acquired pneumonia will rise, life-threatening septicemia will become a greater concern in abdominal surgery, and the risks of opportunistic infections will be the limiting factor for patients undergoing cancer treatments and transplant surgery. According to World Health Organization estimates, new antibiotic-resistant strains have claimed more lives than HIV, influenza, and traffic accidents combined in the past decade. The infections are caused by members of gram-positive bacteria, including methicillin- and vancomycin-resistant *Staphylococcus aurues* (MRSA and VRSA), multidrug-resistant and extremely drug-resistant *Mycobacterium tuberculosis* (MDR-TB and XDR-TB), and *Clostridium difficile*.[1] Most recently, the emergence of the gram-negative enterobacteria and vibrio species carrying the New Delhi metallo-β-lactamase-1 (NDM-1) gene not only left infected patients untreatable by the last line of drug, carbapenem, but also raised worldwide concern over the spread of the resistant gene through the transmissible plasmid.[2]

***Figure 1***
The depleting antibiotic pipeline. Antibiotic development suffered a long draught between 1970-2001. *: topical application.



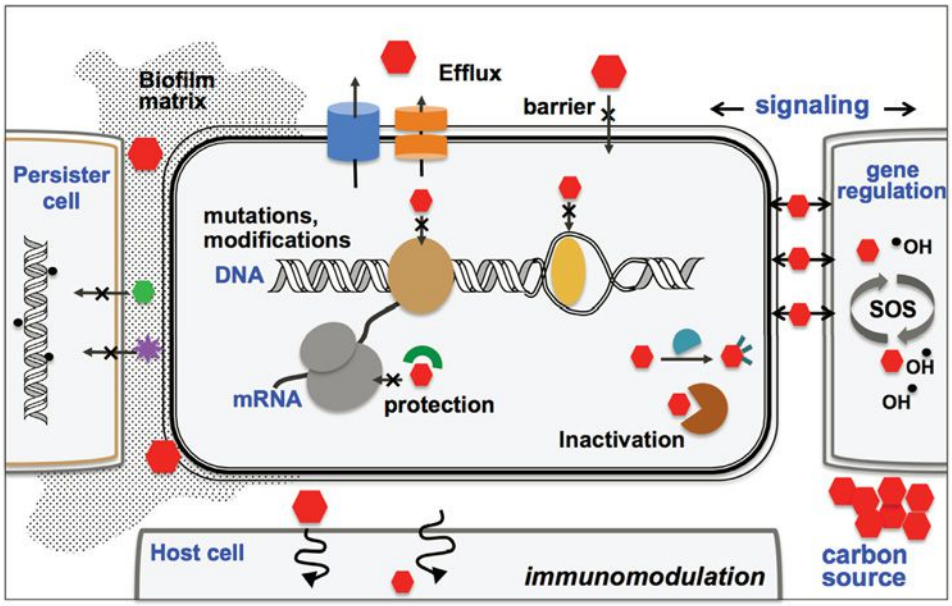

## Falling Behind the Bugs

Antibiotics are generally prescribed in restricted quantity and for a short period, so the profits associated with new antibiotic discovery are considered much less lucrative than those associated with long-term treatments for chronic diseases such as cardiovascular diseases and diabetes. However, that is not to say that the pharmaceutical industry lacks incentive solely due to financial burden and lengthy regulatory hurdles. In reality, the development of novel antimicrobial drugs is scientifically daunting. Almost all new drugs approved after 1990 were either complete synthetic (oxazolidinones) or semi-synthetic derivatives of existing scaffolds originated from soil-dwelling actinomycetes (See Figure 1).[1,3] The discovery of new classes of antibiotics with distinct scaffolds and novel modes of action has been constrained by the lack of chemical diversity in current combinatorial libraries, the narrow scope of structural- and target-based screening approaches, off-target signals in whole-cell screening, and poor success in developing effective screens to validate potential targets that were identified through comparative genomic analysis.[1,4]

## Mechanisms of Antibiotic Resistance and Tolerance

There are hundreds of antibiotics on the market, but they are very similar in that they each interfere with microbial cell growth by inhibiting only a handful of drug targets. These sites are usually macromolecules of essential biosynthesis pathways, such as the ribosome (protein synthesis), topoisomerase, DNA and RNA polymerase (nucleic acid synthesis), cell wall and membrane (peptidoglycan and lipid synthesis), and dihydrofolate reductase (folate metabolism) (See Figure 2).[3] Not surprisingly, antibiotic resistance often evolves by reprogramming and camouflaging these targets through at least four general mechanisms: immunity, efflux, target modification, and drug inactivation. Some bacteria are immune to a drug simply because they have an impermeable barrier or produce protective proteins (TetM and FusB) that mask the drug binding sites. Active efflux involves multidrug resistance transporters that eject antibiotics directly to the outside of the cells or secrete them into the periplasm. Degradation and covalent modification can disarm the antibiotics. Furthermore, modifications of the target entail mutations in the target proteins or enzymatically modifying the targets that disable

***Figure 2***
Multiple roles of antibiotics in natural and clinical environments and the mechanisms of resistance.




drug binding, for example, by methylation of the ribosomal RNA (See Figure 2).[3,5,6]

Research in our lab focuses on studying the molecular mechanism of resistance mediated by rRNA methylation that is induced by subinhibitory concentrations of antibiotic. In staphylococci and streptococci, the *erm* genes encode for the methyltransferase enzymes that modify the drug target in 23S rRNA of the bacterial ribosome and reduce antibiotic binding. The expression of *erm* is regulated at the translational level by at least one upstream leader peptide via an unusual ribosome stalling mechanism. A threshold concentration of antibiotic, such as erythromycin, binds to a ribosome translating the leader peptide and causes the ribosome to stall. The stalling denatures an inhibitory mRNA hairpin in the intergenic region that masks the translation initiation site of *erm* and thereby facilitates the synthesis of Erm enzyme.[7] Clinical studies have shown that Erm leader peptides are highly diverse and the antibiotic inducibility is drug type-specific, but the underlying mechanism is poorly understood. Our major goal is to understand the selective induction of antibiotic resistance in different *erm* homologous systems, specifically to compare the molecular interactions of the regulatory leader peptide with the ribosome in the presence and absence of antibiotic ligands. The work could potentially lead to rational drug design for non-inducer antibiotics.

In some cases, antibiotic tolerance arises when the microbes are able to withstand the drug killing effect by an altered metabolic pathway, such as an attenuation of hydroxyl radical production. This observation has provided an explanation on how seemingly unrelated genetic mutations away from a primary target can result in increased drug tolerance.[8,9] Because most antibiotics are derived from bacterial natural products, the producers possess self-defense mechanisms that contribute to resistance. Recent studies have shown that horizontal gene transfer is extensive between environmental, clinical, and commensal bacteria by means of plasmids, transposons, integrons, and bacteriophages. Widespread antibiotic use is another complication, which exerts strong selective pressure in bacterial population and consequently induces mutagenesis in hypermutator strains. This evolution encourages the formation of persister cells that usually survive in biofilms (bacterial aggregates) (See Figure 2)[6,10] and has hampered the complete eradication of pathogens during chronic infections.

## Reservoirs of Antibiotic Resistance

According to a recent survey from the FDA, approximately 13.1 million kg (~80%) of antimicrobial drugs in the United States are sold for animal husbandry and fisheries annually. In contrast, only 3.3 million kg are administered for human use.[11] Nontherapeutic and subtherapeutic uses of antibiotics in agribusiness began in the 1950s for inclusion in feed and water for poultry and livestock to prevent disease and to promote growth. The application fattens the animal faster and helps to mitigate the impact of disease spread because animals are regularly raised in crowded, unsanitary, and stressful conditions. The result is reduced cost of time and feed. Recognized scientific studies have repeatedly shown that low-dose antibiotics not only propagate resistant bacteria, but also disseminate

these strains into nearby communities as well as the food supply.[6,12-14] During the last few years, the new MRSA strain CC398 and a multidrug resistant strain of *Salmonella enterica* serovar Heidelberg have been found in high abundance in US retail turkey products, farm animals, and even humans who have had no direct contact with the animals.[14] Resistant determinants are also widespread in soil, sewage, and water systems, at high prevalence compared with background resistance in nature.[12,13,15,16] The example of bidirectional zoonotic exchange is an alarming sign of inadvertent creation of resistant strains that are too powerful for current medicine, given that the seven classes of antibiotics used in livestock production are also commonly used in treating human infections. To help preserve long-term effectiveness of medically important antimicrobials, FDA officials in April 2012 called for a voluntary halt to the routine use of several performance-enhancing antibiotics except for circumstances where prescription of such drugs is needed to treat and control animal illness. While farmers and stakeholders have argued tenaciously that eliminating antibiotics would result in larger economic loss and have little or no impact on reducing human infections, alternatives to antibiotics in agriculture should be explored in the United States. Approaches such as improving livestock hygienic practices and reducing overcrowding have had substantial success in Europe in the decades following the bans of antibiotics in animal production.

## Multiple Roles of Antibiotics in Non-Clinical Settings

The popular press tends to paint microbes as disease-causing agents that should be eliminated using antibiotics, and that the role of antibiotics is to inhibit the cohabitating competitors. In contrast to these conventional views, a growing body of evidence has demonstrated that antibiotics serve a role far beyond that of a direct weapon. It has been shown that all antibiotics, regardless of their target and mode of action, exhibit the phenomenon of "hormesis" that is manifested by biphasic response of high-dose inhibition and low-dose stimulation.[17]

At subinhibitory doses, the concentration likely to be found in the environment, antibiotics act as signaling molecules to modulate gene expression and intercellular signaling (See Figure 2).[8,17-19] For instance, aminoglycoside (AG) antibiotics such as tobramycin could interact with the AG response regulator and trigger secondary messenger cyclic diguanylate, which in turn leads to biofilm formation.[20] In another example, subtherapeutic antibiotic treatment of young mice increased the metabolic activity of their gut microbiome by altering the expression of genes involved in the conversion of carbohydrates to short-chain fatty acids.[21] Furthermore, bacterial cells exposed to subinhibitory concentrations of different antibiotics displayed distinct transcription profiles that are associated with pleiotropic effects in metabolic processes.[17,22] Of note, it was found that the production of hydroxyl radicals induced by low antibiotic treatment could generate subpopulations of mutant strains that are resistant to other antibiotics but not the one applied.[8] The isolation of naturally occurring bacteria that can subsist on both natural and synthetic antibiotics as a sole carbon source (See Figure 2)[23] further expands the unrecognized role of antibiotics within bacterial communities. These discoveries have ignited the idea of removing antibiotic "pollution" from the environment by using the bacteria's ability to devour antibiotics. Finally, quorum-sensing molecules that are important for mediating intra- and interspecies communication could exhibit antimicrobial activity at high concentrations,[24] which further illustrates the common dual role of naturally occurring small molecules and suggests a potential resource for antimicrobial discovery.

## Immunomodulatory Benefits of Macrolide Antibiotics

Relatively little is known about the beneficial effects of antibiotics on eukaryotic cell responses, except for the adverse effects usually associated with drug toxicity or compromised innate immunity. Interestingly, long-term macrolide prophylaxes are common pulmonary practices for the treatment of patients with chronic airway diseases, such as chronic obstructive pulmonary disease (COPD) and diffuse panbronchiolitis (DPB). Macrolides belong to the polyketide class of antibiotics that exert their bacteriostatic efficacy by inhibiting protein synthesis. Although the reduction of airway inflammation can in part be attributed to the antimicrobial activity of macrolide, the effects are believed to be negligible because the treatment dosage is too low to fight infection. The biological effects of macrolides are multifaceted but the exact mechanism is not well understood. They have been found to modulate (attenuate) the production of pro-inflammatory cytokines, to reduce epithelial expression of adhesion molecule, and to enhance phagocytosis and

inhibition.[25,26] Development of a macrolide-based anti-inflammatory drug devoid of the antimicrobial properties is currently of potential clinical interest.

## The Future is an Arms Race: Bugging Out

Preventing and controlling infectious diseases relies on widespread collaboration in drug discovery, the judicious use of available antibiotics, improved hygiene, and well-developed methodologies for disease diagnosis. At the top of the list is drug discovery, which is essential to the long-term success of combating disease and requires a reinvigorated search in underexplored microbial niches. Robust screens designed to avoid rediscovering known scaffolds, leveraging existing libraries of synthetic molecules, and exploring the metagenomics approach to access the secondary metabolites from unculturable bacteria are all equally important components in drug discovery in need of further refinement.

In the short-term, antibiotic combination therapies that generate synergistic effects may slow the rise of resistance. To conserve drug effectiveness, tighter regulation on misuse and abuse of antibiotics must be imposed. More efficient and precise diagnostic tools tailored for individual patients will help guide more appropriate drug therapies based on the identified pathogen. Ultimately, it is through research and understanding of the microbes and the biological effects of each molecule at the metabolic level within the cell and within the microbial communities that will lead to new insights into antibiotic design. With an ever-greater range of new genomic and chemical biology tools, the race against antibiotic resistance is just the beginning of a new era for modern medicine.

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## Disclosure

None reported.

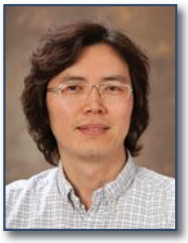
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SAINT LOUIS UNIVERSITY

# Quest for New Biomarkers in Atherosclerosis

*by Yoonsang Cho, PhD & Ángel Baldán, PhD*

**MIF inhibitors analysis will allow us to identify pathophysiological signaling events and involved molecules, which have not been detected by traditional methods.**





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## Abstract

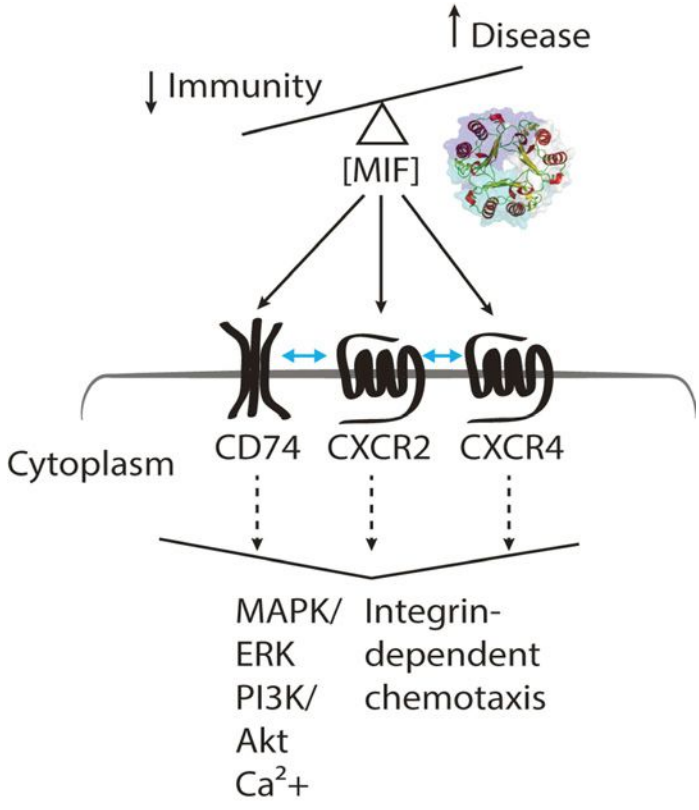
**The Cho and Baldan labs focus their efforts on novel pathways that control atherogenesis. MIF (Macrophage migration inhibitory factor) recruits macrophages to atherosclerotic lesions and activates the production of matrix proteinases, which in turn destabilize atherosclerotic plaques. On the other hand, miR-33 coordinates the expression of several sterol transporters essential for high-density lipoprotein metabolism and bile secretion. Thus, both MIF and miR-33 are promising therapeutic targets to manage patients at risk of developing atherosclerosis.**

## Macrophage Migration Inhibitory Factor in Atherosclerosis

A proinflammatory cytokine called macrophage migration inhibitory factor (MIF) consists of 115 amino acids and exists as a trimer in physiological conditions (See Figure 1). From the historical experiments by John David in 1964, MIF was discovered as the first lymphokine attracting immune cells such as macrophage, T, and B cells.[1] Since then, protective roles of MIF in the immune system have been reported, including the fact that MIF deficient mice are more susceptible to the infection of *Leishmania major* than the wild-type.[2] In contrast, high levels of MIF were observed in major inflammatory diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and atherosclerosis.[3] MIF activates the expression of various proinflammatory cytokines and chemokines. This activation implies that MIF is a master regulator of inflammatory responses in the human body. Intriguingly, MIF has a catalytic activity, missing in canonical cytokines and chemokines, and converts a C-O double bond into a single bond and vice versa.[4] It is not clear whether this catalytic activity is physiologically relevant. This catalytic activity has been used as a molecular trap to identify small molecules binding to MIF.[5]

Migration of mononuclear leukocytes is one of the key features of atherosclerosis. MIF recruits macrophages to the site of atherosclerosis and activates them to produce matrix metalloproteinases, which in turn degrade collagen fibrils, providing mechanical strength to atherosclerotic plaque.[6] As the instability of the plaque is directly related to the progression of the disease, MIF inhibitors could be

***Figure 1***
MIF signaling. Crystal structure of a trimeric MIF is shown in cartoon representation. Surface of each monomer is colored differently. Up and down arrows indicate the increase and decrease of disease severity and immunity, respectively, proportional to the physiological concentrations of MIF. Blue bi-directional arrows between the receptors indicate the interaction between the MIF receptors. The large downward arrowhead indicates cellular outcomes of the receptor signals activated by MIF.




potential therapeutics for atherosclerosis in combination with drugs targeting other disease factors, including cholesterol, which is under investigation by the Baldán lab. To achieve this goal, understanding the molecular mechanism of MIF–mediated cell migration is essential.

## MIF-receptor Signaling

MIF binds to an invariant chain of MHC class II CD74, canonical chemokine receptors CXCR2 and CXCR4.[7] Since CD74 is lacking a signaling domain, it forms a hetero-dimer with CD44, which then interacts with intracellular signal transducers (e.g., src-kinases) and activates downstream signaling pathways (e.g., MAPK, ERK, and AKT). CD74 can form a heterodimer with CXCR2 and CXCR4[8] to mediate various MIF signaling in any given environment. In general, chemokine-receptor interaction is complicated due to their promiscuous binding patterns. For instance, MIF receptor CXCR2 and HIV co-receptor CCR5 can recognize seven chemokines, and they have been implicated in atherosclerosis.[9,10] Furthermore, chemokine receptors, belonging to the type A G protein coupled receptor (GPCR) family, can bind to several different G-proteins (e.g., $G_i$, $G_s$, $G_q$, $G_{12}$, etc.) depending on ligands and co-factors. Very little is known about the molecular mechanism of MIF-receptor interaction and their cellular outcomes. We are currently investigating these by employing multidisciplinary means, including structural biology, chemical biology, and label-free cell-based assay.

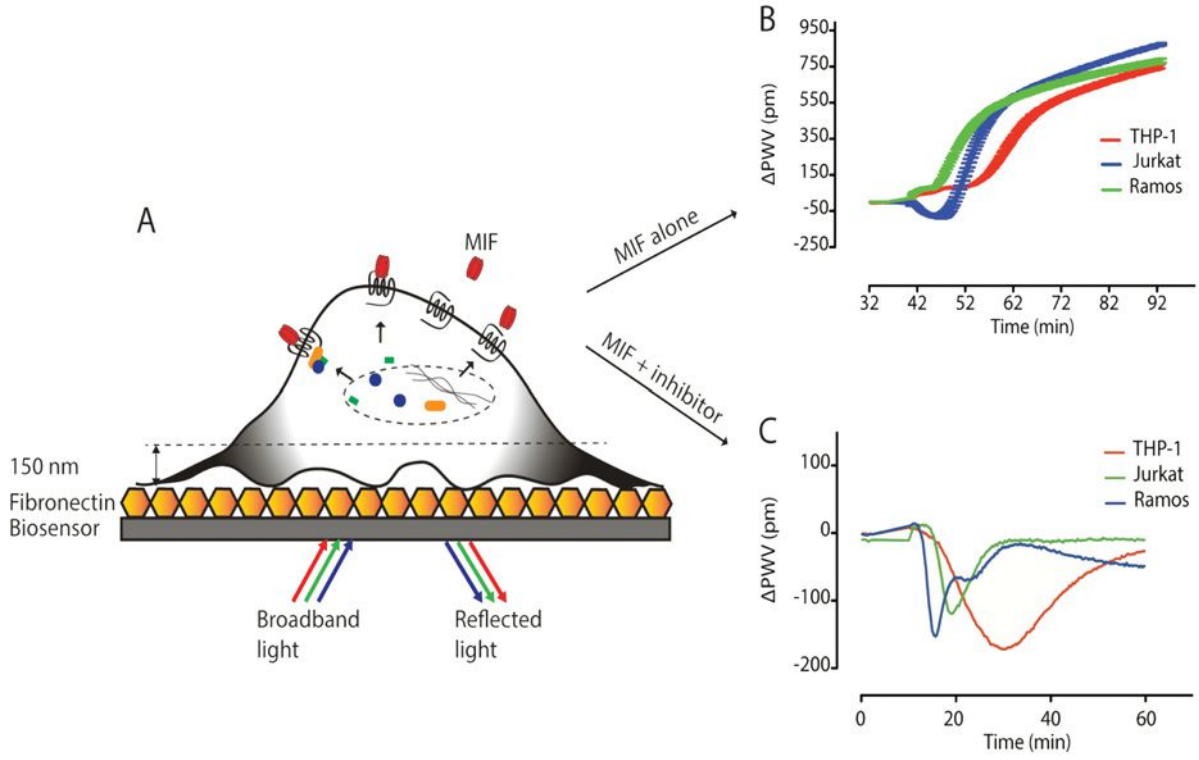
## Small Molecule MIF Modulators

Some of the prototypic catalytic MIF inhibitors exhibited inhibitory effects against the immunological functions of MIF.[11] Inspired by this, we identified two dozen structurally and chemically diverse catalytic MIF inhibitors through high-throughput screening (HTS) of small molecule libraries. Several inhibitors were crystallized in complex with MIF and revealed covalent and non-covalent binding to the first amino acid, proline. Interestingly, some of them exhibited a non-competitive inhibition pattern, indicating that they might not bind to the catalytic site but bind to another part of MIF. In our recent study, a novel allosteric binding site was discovered from the complex crystal structures of MIF and ibudilast, which had been used as an asthma drug for two decades in Japan. We also tested whether the inhibitors modulate MIF-mediated cell responses. Indeed, different inhibitors altered the MIF-mediated cell responses in distinctive ways. We are investigating which receptors and signaling pathways were affected and using these small molecule MIF modulators as molecular probes for further mechanistic studies.

## Innovation in MIF-receptor Interaction Study

We are currently identifying MIF residues critical for receptor binding to ultimately link this information to the resulting intracellular signals in leukocytes and lymphocytes. We employ X-ray crystallography to obtain atomic resolution of the molecular structures of MIF in complex

***Figure 2***
Label-free technology for monitoring cellular events. (A) MIF (red) binds to receptors on the cell surface and activates the intracellular signaling events represented as dynamic mass redistribution (DMR, black indicates movement of signaling molecules). Cells are plated on a fibronectin-coated biosensor. (B) DMR is represented as the peak wavelength value difference (delta PWV) before and after the addition of MIF. (C) One of the HTS MIF inhibitors alters the MIF-mediated DMR responses compared to those of MIF alone in panel B.




with its inhibitors. Among the MIF receptors, CXCR2 and CXCR4 are 7-transmembrane proteins, and it is difficult to work with them *in vitro*. One of the classical ways of studying GPCR is artificially replacing a downstream target gene with a reporter gene to monitor the activation of the receptor of interest. With this reporter-based assay, one can monitor limited cellular events at only a single time point. To overcome this limitation, we have established a label-free technology that measures holistic cellular response in real-time (See Figure 2A). We successfully measured dynamic mass redistribution (DMR; relocation of intracellular molecules upon the ligand-induced activation of receptor) from MIF-treated cell lines. Three different immune cell lines, THP-1 (monocyte), Jurkat (T cell), and Ramos (B cell), were activated with MIF and generated distinctive DMR patterns (See Figure 2B). B cells reacted at the earliest time points, T cells the second, and monocytes the latest. In addition, T cells responded in a negative mode at earlier time points and shifted to a positive mode. Opposite DMR modes and the amplitudes of the responses imply the activation of distinctive signaling molecules and pathways in each cell line.

To identify the signaling molecules and pathways involved, we perform the label-free assay in the presence of signaling molecule/pathway-specific inhibitors. Evaluation of small molecule agonists and antagonists in physiologically relevant conditions is one of the advantages to using this technology. Different catalytic MIF inhibitors altered the DMR responses of different cell lines in distinctive ways (See Figure 2C). We are planning to use this highly sensitive label-free technology to work with primary cells from disease patients. This analysis will allow us to identify pathophysiological signaling events and involved molecules, which have not been detected by traditional methods.[12]

## Future Direction of MIF Research in Atherosclerosis

One of our research interests is the molecular mechanism of MIF-receptor interaction in chronic inflammatory conditions, including atherosclerosis. Since

cell surface receptor composition varies depending on disease, understanding the molecular details of the ligand-receptor interaction and associated cell signaling pathways is essential to fine-tuning pathological immune responses with minimal adverse effects to normal physiological events. We will investigate MIF-receptor interaction in atherosclerotic macrophages and identify the receptors involved in the pathogenesis. Based on this information, we will design small molecule antagonists interfering with the MIF-receptor interaction. Collected basic findings will be tested *in vivo* using animal models of atherosclerosis. Our translation research, especially in collaboration with physician scientists, will greatly contribute in the treatment of atherosclerosis.

## Atherosclerosis and MicroRNAs

Atherosclerosis is a progressive disease of the artery wall where large numbers of monocytes infiltrate the sub-endothelial space and subsequently differentiate into macrophages and become lipid-loaded. At later stages, more advanced plaques develop, containing inflammatory cells, a necrotic core, and a fibrous cap. When unstable plaques rupture, a thrombotic event is initiated that ultimately results in heart attack, stroke, or peripheral artery disease. According to the American Heart Association, atherosclerosis-related cardiovascular disease accounts for > 30% of all deaths in the U.S.[13] The exact cellular and molecular events that lead to the early development and progression of atherosclerotic lesions are not yet completely understood, but several risk factors have been identified in large population studies. For example, the Framingham Heart Study recognized elevated cholesterol in blood as a risk factor for heart attack in 1961. Since then, great progress has been made to understand the regulation of both intracellular cholesterol homeostasis and lipoprotein metabolism.

Our laboratory is interested in the regulation of sterol and triglyceride homeostasis by microRNAs (miRNAs), which are small, non-coding 20-24 nt RNAs that promote the silencing of their target genes by binding to specific, partially complementary regions in the 3'-UTR (untranslated regions) of the target mRNA.[14] This binding results in RNA interference and/or translational repression of the target gene.[14] miRNAs can be expressed from their own promoter or can be encoded within the introns of other genes (so they are expressed when the "hosting" mRNA is transcribed). Regardless, the original miRNA transcript (Pri-miRNA) is sequentially cleaved by the exonucleases, Drosha (nuclear) and Dicer (cytoplasmatic), to generate the Pre-miRNA (100-150 nt) and the mature miRNA (20-24 nt) molecules, respectively. It is the mature miRNA that is finally incorporated into the RNA-Induced Silencing Complex (RISC).[14] Other, "non-canonical" pathways that are independent of Drosha or Dicer have also been described. Nevertheless, the expression of a particular miRNA can be tissue, developmental, and even disease–specific, revolutionizing our understanding of epitranscriptional regulatory networks. Multiple studies have shown that miRNAs function as key mediators in multiple normal and disease-related biological processes.[15-17] Consequently, novel therapeutic approaches that exploit miRNA–dependent gene silencing offer a promising future for the management of multiple diseases.

## HDL-cholesterol and miR-33

In 2010, five different laboratories, including ours, reported on miR-33.[18-22] This miRNA is expressed from within an intron of SREBP-2, a transcription factor that functions as a master regulator of intracellular cholesterol homeostasis promoting the expression of cholesterogenic genes (including HMGCR, the rate-limiting enzyme of the cholesterol biosynthetic pathway), the LDL-Receptor, PCSK9, and other cholesterol-related genes. The clinical importance of the SREBP-2 pathway is revealed in patients taking statins to decrease plasma LDL-cholesterol levels. We[20] and others[18,19,21,22] showed that the expression of miR-33 is physiologically regulated by the levels of intracellular cholesterol (induced by sterol depletion and suppressed by sterol loading) and stimulated by treatment with statin drugs, both *in vitro* and *in vivo*. These initial studies also showed that miR-33 functions to repress the expression of the cholesterol transporter ABCA1, and identified the sequences in the 3'UTR of ABCA1 that bind to miR-33.[18-22]

ABCA1 plays a critical role during the early steps of high-density lipoprotein (HDL) biogenesis by mobilizing intracellular cholesterol towards ApoA-1 in circulation, and patients with functional mutations in this transporter develop hypoalphalipoproteinemia (low HDL-c levels) or, in the most severe cases, Tangier disease (< 5% normal HDL-c levels).[23] Consequently, mice in which we overexpressed miR-33 (via adenoviral transduction) showed decreased hepatic ABCA1 levels and reduced circulating HDL-c levels, compared to control animals.[20] More importantly, the opposite was also true: silencing hepatic miR-33 (by using antisense oligonucleotides) led to elevated

hepatic ABCA1 mRNA and protein levels and elevated HDL-c in blood, compared to control mice.[18-20] These results suggested that sustained silencing of hepatic miR-33 might be used therapeutically in hypercholesterolemic patients to raise the levels of anti-atherogenic HDL-c and thus reduce the risk of cardiovascular disease.

## Bile Secretion and miR-33

We reported that miR-33 also controls the expression of sterol transporters involved in bile secretion, namely ATP8B1 and ABCB11.[24] Severe functional mutations in these transporters result in Progressive Familial Intrahepatic Cholestasis (PFIC) type-1 and -2, respectively.[25] Other, less severe mutations lead to Benign Recurrent Intrahepatic Cholestasis (BRIC) type-1 and -2, respectively.[25] We characterized the miR-33 response elements in the 3'UTR of these genes and showed that manipulation of hepatic miR-33 levels in mice (by using adenoviral vectors or antisense oligonucleotides) results in changes in bile secretion rates and overall bile collection from the gallbladder.[24] Additionally, we showed that treating mice with both a statin and a Pagen diet (a high fat, high cholesterol, sodium cholate diet) resulted in a cholestatic phenotype, compared to mice that were fed the diet but did not receive the drug. Importantly, this liver phenotype could be rescued by pre-treatment with anti-miR-33 oligonucleotides,[24] suggesting that miR-33 could mediate some of the effects of statins *in vivo*.

## Reverse Cholesterol Transport and miR-33

Collectively, the data discussed above suggest that miR-33 is physiologically induced by sterol depletion, prevents the loss of intracellular sterols, and controls the expression of sterol transporters via both the basolateral membrane (via ABCA1 towards HDL lipoproteins) and the apical membrane (via ATP8B1 and ABCB11 towards the bile). Both HDL and bile metabolism are essential components of the Reverse Cholesterol Transport (RCT) pathway, which mobilizes extra-hepatic cholesterol towards the liver for subsequent biliary secretion and ultimately loss through the feces.[26] While this pathway is a very inefficient way of removing sterols (> 95% bile acids are reabsorbed in the intestine and shuttled back to the liver), it is the main mechanism we have to remove excess cholesterol (the other main pathway is known as Trans-Intestinal Cholesterol Excretion-TICE).

The RCT is predicted to be atheroprotective, by facilitating the removal of sterols from macrophages in atheromata.[26] We[24] and others[27] showed that an acute (two to four week) treatment of either wild-type or atherosclerosis-prone *Ldlr*$^{-/-}$ mice with anti-miR-33 oligonucleotides resulted in accelerated RCT *in vivo*, compared to mice treated with control oligonucleotides. In these experiments, mice receive an intraperitoneal injection of macrophages loaded with radiolabeled cholesterol, and the RCT is estimated by the recovery of radiolabeled sterols in blood, liver, gallbladder, and feces. Collectively, these data provided further support to the hypothesis that silencing miR-33 in hypercholesterolemic patients might prevent cardiovascular events.

## Challenging the miR-33 Hypothesis: When All that Glitters Is Not Gold

Studies in non-human primates showed that a 16-week treatment with anti-miR-33 oligonucleotides increased plasma HDL-c, while at the same time reduced VLDL-triglycerides.[28] These latter authors also reported that a 4-week antisense treatment following 16-weeks of a high fat, high cholesterol feeding accelerated the regression of atheromata in *Ldlr*$^{-/-}$mice.[27] A recent report showed that miR-33/*ApoE* double knock-out mice had decreased atherosclerosis, compared to atherosclerosis-prone *ApoE*$^{-/-}$ mice.[29] In contrast, we recently showed that long-term (12-week) treatment of *Ldlr*$^{-/-}$ mice with anti-miR-33 oligonucleotides did not change the size or composition of atheromata, compared to mice receiving control oligonucleotides or saline.[30] These latter results are paradoxical, especially when considering the fact that previously described miR-33 targets (e.g., ABCA1, ATP8B1, ABCB11, and others) were induced in the livers of mice receiving the antisense,[30] as expected. Also intriguing is the fact that by the end of the three-month experiment, the plasma levels of HDL-c were not significantly different among the different treatments, and that VLDL-triglycerides were indeed increased in mice receiving anti-miR-33 treatment.[30] The different outcome between the four-week *regression* study[27] and our twelve-week *progression* study[30] need to be elucidated. Differences in the progression of vascular lesions following whole-body miR-33 deficiency[29] or treatment with anti-miR-33 oligonucleotides[30] are also intriguing, and might reflect the impact of miR-33 expression in several cell types (hepatocytes, macrophages, endothelial cells). It is conceivable that anti-miR-33 therapy could be effective

in some, but not all, cell types where miR-33 is normally expressed. It will also be important to establish whether different chemistries alter the bioavailability and potency of anti-miR-33 oligonucleotides in either liver or lesions.

## What We Missed in Mice

It is important to note that primates, but not rodents, express a second miR-33 gene (miR-33b) from an intron of *SREBP-1*. Hormones, dietary challenges, and even statin treatment differentially regulate *SREBP-1* and *-2*, and this control may be critical to fully understanding the role of miR-33a/b in lipid homeostasis, since the expression of miR-33a and miR-33b is expected to parallel that of their hosting gene. In marked contrast to our atherosclerosis study,[30] a longitudinal study in non-human primates did show a sustained elevation of HDL-c, as well as a strong decrease in triglycerides.[28] Whether the differences in cholesterol and triglyceride metabolism between mice and primates in response to anti-miR-33 treatment are due to miR-33b remains to be established, but anti-miR-33 oligonucleotides should block the action of both miR-33a and miR-33b.

The discrepancies between rodent and primate models thus raise an important concern regarding the direct translation of data from rodent models to human physiology and metabolic disorders. Using a combination of *in vivo* experiments and cell culture techniques, we are currently exploring other metabolic pathways that respond to miR-33a/b overexpression or silencing that might explain the specificities between mice and primates.

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# Almost Everyone Over 50 Should be Put on a Statin to Reduce the Risk of Cardiovascular Disease: *A Protagonist View*

*by Pratik Sandesara, MD & Douglas B. Bogart, MD*

***We believe the data presented here show that the immense burden of cardiovascular disease in the United States can be reduced by starting almost everyone over the age of 50 on statin therapy.***



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## Abstract

**The burden of cardiovascular disease (CVD) in the United States (U.S.) and worldwide is immense. The total cost for CVD care in the U.S. for 2010 was over 400 billion dollars.[1] The levels of total cholesterol and low density lipoprotein cholesterol (LDL-C) are critical determinants for the development of CVD.[2] It has been clearly established that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statin drugs), are potent LDL-C lowering agents that are the cornerstone of CVD treatment. We will review here the developing evidence to support statin therapy for primary prevention of cardiovascular disease for almost everyone over the age of 50.**

## Introduction/Background

CVD encompasses the diagnoses of coronary heart disease (CHD) as well as hypertension, heart failure and stroke. Approximately 83 million Americans have CVD and of those, 16 million have known CHD.[1] CVD is the leading cause of death accounting for one out of every three deaths.[1] Of these deaths nearly 70% are due to CHD and stroke[3] and the risk of either process is in part related to the levels of total cholesterol and LDL-C. Current guidelines on LDL-C goals and the use of LDL lowering therapy for primary prevention are based on an individual's absolute risk for CHD (See Table 1) which is from the Adult Treatment Panel III (ATP-III).[4,5] For individuals with known CHD or coronary risk equivalents (a 10-year risk >20%), the LDL-C goal is <100 mg/dL but < 70 mg/dL is a reasonable option for the clinician.[5]

The recognized coronary risk equivalents include diabetes mellitus, symptomatic carotid disease or an asymptomatic lesion with > 50% stenosis, and peripheral arterial disease or abdominal aortic aneurysm. Persons with 2+ risk factors who have a 10-year risk of CHD >20% are also

Table 1
Current Treatment Guidelines (Modified from Reference #4).

| RISK CATEGORY | LEVEL OF RISK | LDL-C GOAL | OPTIONAL LDL-C GOAL |
|---|---|---|---|
| KNOWN CHD | HIGH >20%/10 years | < 100 mg/dL | <70 mg/dL |
| CHD RISK EQUIVALENT (Diabetes mellitus, PAD or AAA, Symptomatic carotid disease or > 50% stenosis, or 2+ risk factors and CHD >20%/10 years | HIGH >20%/10 years | <100mg/dL | <70 mg/dL |
| 2+ RISK FACTORS | Intermediate 10-20%/10 years | <130 mg/dL | |
| 0-1 RISK FACTOR | LOW <10%/10 years | <160 mg/dL | |

considered as a coronary risk equivalent and hence a viable LDL-C goal is < 70 mg/dL. Individuals with multiple (2+) risk factors and 10-year risk between 10% and 20%, the LDL-C goal is <130 mg/dL but an LDL-C <100 mg/dL is also a therapeutic option.[4,5] For individuals with a 10-year risk <10%, the LDL-C goal is < 160 mg/dL as it is for those with 0-1 risk factor.[4] The current recommendations for initial therapy from the ATP-III report emphasizes therapeutic lifestyle changes (TLC) including reduction in the intake of saturated fats and cholesterol as well as a regular exercise program. Unfortunately, the TLC are frequently not enough to achieve the desired therapeutic results. In fact the average amount of cholesterol reduction that can be expected by TLC is about 10%.[6]

The basis of cardiovascular risk assessment for primary prevention is a risk score calculation utilizing cardiac risk factors. Risk scores have been developed for both CHD and CVD. The most frequently used are the Framingham risk scores (FRS) or Reynolds (RRS) risk scores.[7] The FRS for CHD provides the basis for the risk assessment in the Adult treatment Panel III.[4,5] While the original FRS predicted the 10-year risk of CHD events,[8] the score has been expanded to predict the 30 year risk of cardiovascular disease events including coronary death, myocardial infarction and stroke.[9] The RRS is a CVD risk score that is gender specific and includes the measurement of hs-CRP. The major differences between the FRS both for CHD alone and CVD as well as the RRS are shown in Table 2.

It is important to recognize that the FRS continues to be extremely valuable in the risk stratification process. It allows the clinician to focus on the individual risk factors for each patient and thus potentially facilitating optimal evaluation and treatment of each abnormality. However, there are inherent limitations in all the risk score estimations.[10] The FRS, for example, was derived from a single center with predominantly Caucasian patients. Risk prediction in a younger age group is problematic because of the low absolute risk in this group when the time frame is 10 years. The 30-year or even the lifetime risk estimate is more useful for this group.[11] Two studies have reported on patients with acute myocardial infarction (AMI) and found that the majority of the patients were not high risk using the FRS thus further emphasizing the limitations of the current risk assessment instruments.[12,13]

Because of the constraints of the risk calculators other modalities have been used to help with the risk stratification process. Both coronary artery calcium (CACS) and carotid-intima media thickness (CIMT) have been reported to identify individuals who have early atherosclerosis. Both of these tests have been given a IIa recommendation by the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults.[7]

The goal of this additional testing is to identify individuals with subclinical atherosclerosis during the long latent period of CVD before it becomes manifest with symptoms and events. Fatty streaks and manifestations of CHD were seen at autopsy in United States soldiers ages 30 years and younger who were killed in the Korean war.[14] In an effort to determine the optimal approach in younger patients with potential early atherosclerosis CIMT and CACS were evaluated in patients between ages 36-59.[15] These investigators found that CIMT detected early

Table 2
Comparisons of the Commonly Used Risk Scores (Modified from References 5 and 7).

| | FRS for CHD | FRS for CVD | RRS for CVD♂ | RRS for CVD♀ |
|---|---|---|---|---|
| Risk factors evaluated | Age, gender, total cholesterol, HDL-C, Smoking, Systolic blood pressure, antihypertensive medication | Age, gender, total cholesterol, HDL-C, Smoking, Systolic blood pressure, antihypertensive medication, diabetes mellitus status | Age, gender, total cholesterol, HDL-C, Smoking, Systolic blood pressure, parental history of MI at age < 60 yr, hsCRP | Age, gender, total cholesterol, HDL-C, Smoking, Systolic blood pressure, parental history of MI at age < 60 yr, hsCRP |
| End points for score | CHD: Death and MI | Coronary Death, MI, Stroke | MI, Stroke, coronary revascularization, CVD death | MI, Stroke, coronary revascularization, CVD death |
| Duration | 10 year | 30 year | 10 year | 10 year |

atherosclerosis in patients with low FRS and zero CACS and thus may be more sensitive for detection of minimal disease in this group of patients. Clearly more studies are needed to determine if subclinical atherosclerosis can be reliably and economically detected so that evaluation and treatment can be directed at the population most likely to benefit.

At the present time because of the uncertainty of the risk models and lack of proven definitive supplemental testing, it has been suggested that age could be used as a threshold. Wald et al. found that age screening using a threshold of ≥ 55years had an equal detection rate with the FRS for first time CVD events (86%) and a false positive rate of 24% compared to 21% for FRS.[16] These authors concluded that screening by age was easier and gave essentially the same result as using the FRS. For example, if a point of initiation of statin therapy were a 10% or greater risk over 10 years then in England 83% of men over age 50 years and 56% of women over age 60 would qualify for the therapy.[17] This adds credence to the concept of age as a threshold for potential statin therapy.

In the remainder of this paper we will review the current literature on statin use in primary prevention of CVD using age as a guide for the initiation of therapy.

## Statin Use for Primary Prevention

In this section we have briefly reviewed the studies that evaluate statin therapy for primary prevention. These trials are summarized in Table 3.

The West of Scotland Coronary Prevention Study (WOSCOPS)[18] was a randomized, double-blind, placebo-controlled trial involving 6,595 men aged 45 to 64 years with a mean plasma cholesterol level of 272 mg/dL and no previous history of CVD. The mean LDL-C at baseline was 192 mg/dL. Subjects were randomized to pravastatin 40 mg or placebo group. The pravastatin group had a 31% reduction in major CHD events. In addition, the combined outcome of death from definite CHD or definite nonfatal myocardial infarction (MI) was lower in the pravastatin compared to the placebo group (5.5% vs 7.9%; $p<0.001$) after five years. These results were seen with only a 20% reduction in total cholesterol and a 26% reduction in the LDL-C cholesterol.

An extended follow-up of the WOSCOPS cohort approximately ten years after completion of initial trial suggests ongoing benefit of statins after five years of treatment.[19] At the time of the extended follow-up, a large cohort had stopped statin therapy, with only about 40% continuing treatment. Approximately ten years after completion of the initial trial, the combined risk of death from CHD or nonfatal MI was lower in the pravastatin group compared to the placebo group (8.6% vs 10.3; $p=0.02$). Furthermore, over the entire follow-up period of approximately 15 years, the combined risk of death from CHD or nonfatal MI was 11.8% in the pravastatin group and 15.5% in the placebo group ($p<0.001$). No

Table 3
Studies of Primary Prevention with Statins

| STUDY | DESIGN | PATIENTS STUDIED | F/U DURATION | OUTCOME | Therapy @ F/U |
|---|---|---|---|---|---|
| WOSCOPS | Randomized, Double-blind and placebo controlled: Pravastatin 40 mg vs Placebo | 6595 men aged 45-64 yrs. No CHD<br>Ave cholesterol=272 mg/dL and<br>LDL-C=192 mg/dL | 5 years<br><br>15 years | 26% reduction in LDL-C/ 31% reduction in CHD events @15 yrs risk of CHD death or MI ↓ 24% | 40% continued therapy |
| AFCAPS/TexCAPS | As per WOSCOPS but used Lovastatin 20-40 mg vs Placebo | 5608 men (age 45-73)<br>997 women (age 55-73)<br>No CHD/ Ave cholesterol=221 mg/dL and LDL-C= 150 mg/dL | 5.2 years | 25% reduction in LDL-C/Relative risk of CHD event<br>= 0.63 with therapy | 71% adherence to the treatment at the end of trial |
| ASCOT-LLA | As per WOSCOPS Atorvastatin<br>10 mg vs Placebo | Hypertensive patients with ≥3 risk factors<br>10,305 patients (19% women)<br>Ages 40-79 yrs.<br>Mean age 63 yrs.<br>Median LDL-C= 131 mg/dL | 3.3 years | Reduction in LDL-C= 42 mg/dL<br>27% reduction in stroke fatal and non-fatal 36% reduction in non-fatal MI and CHD death | Trial stopped prematurely due to the favorable results<br>87% adherence to atorvastatin |
| CARDS | As per WOSCOPS Atorvastatin 10 mg vs. Placebo | 2,838 patients<br>(32% women) with Type 2 diabetes without known CVD / Mean age ≈62 years<br>Ave LDL-C= 118 mg/dL | 3.9 years | Reduction in LDL-C= 40 mg/dL / 36% reduction in CHD events / 48% deduction in stroke events / 27% reduction in death | Trial stopped prematurely due to the favorable results<br>78% adherence to atorvastatin |
| JUPITER | As per WOSCOPS Rosuvastatin 20 mg versus Placebo | 17,802 patients with LDL-C < 130 mg/dL (median-108 mg/dL) and<br>hs-CRP ≥ 2.0mg/L | Median F/U 1.9 years | Reduction in LDL-C by 50% and hs-CRP by 37% / 44% reduction in CHD events and 48% reduction in stroke events | Trial stopped prematurely due to favorable results<br>>75% adherence to therapy |
| CTT COLLABORATORS | Meta-analysis of 27 randomized trials (22 with statin vs placebo and 5 with different doses of statin) | 174,149 participants and the patients were stratified by risk | Variable in the 27 studies | In persons with a 5 yr. risk < 10% of major vascular event for each 39 mg/dL reduction in LDL-D there was an absolute ↓ in events ≈11per 1000 over 5 years | High adherence rate in the majority of the studies |
| Maccabi Healthcare Services | Retrospective analysis of statin use and nonfatal CHD events in a community population | 171,535 patients in an HMO with mean age of 58 yrs. | Variable as the patients were enrolled from 1998-2009 | Persistent users (≥80%) had a hazard ratio for CHD events of 0.58 compared to the non-persistent users / No data on mortality in the groups | Variable from ≥ 80% to < 20% |

significant difference in adverse events were seen in the two treatment groups.

This trial showed the continued benefits of statin therapy ten years after initiation, even in a large cohort that had stopped treatment after five years. This suggests that the early initiation of statin therapy had long-term benefits for CHD event reduction. This concept is supported by the effect of DNA-sequence variations that resulted in lowered levels of LDL-C.[20] This report found a reduction in the lifetime risk of CHD events related to the genetic mutations that lowered the LDL-C by a modest 28%.

The AFCAPS/TexCAPS[21] was a randomized, double blind, placebo-controlled trial of 6,605 adults (5,608 men and 997 women) that compared lovastatin 20-40 mg daily vs. placebo for prevention of the first major acute coronary event in men and women without evidence of CVD. The participants had mean values for total cholesterol (221 mg/dL), LDL-C (150 mg/dL) and high-density lipoprotein cholesterol (HDL-C) of 36 mg/dL. After an average follow-up of 5.2 years, treatment with lovastatin resulted in a 37% reduction in the incidence of first acute major coronary events ($p<0.001$) and a 40% reduction in incidence of myocardial infarction ($p=0.002$). There was no significant difference in adverse effects in the two treatment groups.

The ASCOT-LLA was a multi-centered randomized trial of 10,305 hypertensive patients who had at least

three other risk factors for CHD.[22] These patients were randomized to one of two anti-hypertensive regimens as well as a second randomization to atorvastatin 10 mg versus placebo. The trial was a high risk group with hypertension as well as ≥ 3 risk factors and the mean age of the group was 63 years. Only 19% of the participants were women. The trial was stopped prematurely due to the favorable outcome in the active treatment arm with a 36% relative risk reduction (RRR) in CHD events and 27% RRR in stroke events. In contrast to other studies this trial showed no benefit in statin therapy in 2,532 patients with diabetes.

In a primary prevention trial of patients with type 2 diabetes (CARDS), individuals without known CHD were randomized to atorvastatin 10 mg versus placebo. [23] There were 2,838 patients in this study with an age range of 40-75 years with an entry LDL-C about 118 mg/dL. A 37% reduction in the rate of CHD events, 48% reduction in stroke events and 27% reduction in death was observed in this trial. The current guidelines recommend a statin drug in patients with diabetes mellitus.

The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial was a randomized, double blind, placebo controlled trial of 17,802 healthy men and women with LDL-C levels <130 mg/dL and elevated high sensitivity C-reactive protein (hs-CRP) level of > 2.0 mg/dL.[24] Subjects were randomized to rosuvastatin 20 mg daily or placebo. Treatment with rosuvastatin resulted in a 44% reduction in primary endpoint of first major cardiovascular event (nonfatal MI, nonfatal stroke, unstable angina, revascularization, and death from cardiovascular causes) ($p<0.00001$), 54% reduction in incidence of fatal and nonfatal MI ($p=0.0002$), 48% reduction in fatal and nonfatal stroke ($p=0.002$), and a 20% reduction in all-cause mortality ($p=0.02$).

The JUPITER trial has been criticized because it was prematurely stopped at a median follow up of 1.9 years and this may have enhanced the treatment benefit. Also the mortality rate was lower than one would have expected. In addition, because the trial was sponsored by a drug company there has been concern expressed of commercial bias.[25] The issue of whether elevations of hs-CRP should be used to justify treatment with statins has also been in question.

The Heart Protection Study (HPS) evaluated the effect of hs-CRP on the benefits of statin therapy in a group of 20,536 patients.[26] This was not primarily a primary prevention trial in that the patients had to be at high risk of vascular events. The group had to have either CHD, peripheral arterial disease, diabetes mellitus or be a male over age 65 years on drug treatment for hypertension. The patients were randomized to simvastatin 40 mg or placebo. In addition they were stratified by the hs-CRP level from < 1.25 mg/l to over 8 mg/l (six groups were assessed). This study found that the hs-CRP level did not influence the benefit of statin therapy and in particular there was benefit in the group with both low LDL-C and hs-CRP. Hence, the HPS found a benefit of statin therapy independent of the levels of LDL-C and hs-CRP.

More recently, the Cholesterol Treatment Trialists' (CTT) Collaborators conducted a meta-analysis of 27 randomized trials with 174,149 participants to study the effect of LDL-C reduction with statin therapy, particularly in individuals at low risk for vascular disease.[27] The data showed that statins reduce the risk of major vascular events by 21% per 1.0 mmol/L(about 39 mg/dL) reduction in LDL-C ($p<0.0001$). More significantly, in individuals with a five-year risk of a major vascular event (non-fatal MI, coronary death, coronary revascularization, or stroke) lower than 10%, reduction in LDL-C with statin therapy resulted in 11 fewer major vascular events per 1,000 over five years. The benefit observed was independent of age, gender and baseline LDL-C and extends to those without previous history of vascular disease, diabetes or chronic kidney disease. There was no observed increased cancer risk or any other non-CVD risk. This report extends the benefits of statins to those at lower risk and these are patients who would not currently be treated based on the present clinical guidelines.

Two other meta-analyses each with more than 65,000 patients (using many of the studies as the CTT collaborators) found that there was a favorable effect on CVD events and mortality in primary prevention with statin therapy.[28, 29] None of the meta-analyses showed significant morbidity from statin use in primary prevention. Another report of "real-world" experience with statin therapy for primary prevention, showed that in a community setting statin therapy reduced acute cardiac events.[30]

## Other Beneficial Effects of Statins

In addition to their well-known and potent LDL-C lowering effect, statins have several other benefits. They are known to have beneficial cardiovascular pleiotropic effects such as atherosclerotic plaque stabilization,

improved endothelial function, increased nitric oxide bioavailability and antioxidant properties independent of cholesterol lowering.[31] Depletion of isoprenoids due to lack of mevalonate is postulated as a cause of the pleiotropic effects.[32]

Statin use is also associated with reduction in cancer risk and mortality in transplant patients independent of cholesterol lowering.[33] In a total of 255 cardiac transplant patients, statin use was associated with decreased incidence of malignancy from 34% to 13% ($p<0.003$) 8 years after transplant and improved cancer-free and overall survival (both $p<0.0001$). In addition in a Danish registry, statin use in patients with cancer was associated with a reduction in cancer mortality.[34] Obviously, this observation needs further study.

Furthermore, statins are also of benefit in persons with chronic kidney disease (CKD). A meta-analysis of 80 trials with 51,099 participants showed that statins reduce all-cause mortality, cardiovascular mortality, and cardiovascular events in patients with CKD not receiving dialysis.[35] There was a statistically significant decrease in the incidence of major vascular events (fatal or nonfatal stroke or MI) by 40-50% and all-cause and cardiovascular mortality by almost 20%.

Rosuvastatin was shown in the JUPITER trial to reduce the incidence of venous thromboembolism without increasing the bleeding rate.[36] Statin use has also been associated with a reduction in the risk of developing open-angle glaucoma.[37] This data was gathered from a large managed care network with 316,182 patients treated with statins for hyperlipidemia.

To summarize, the potential benefits of statin therapy include the pleiotropic effects, cancer reducing effects independent of cholesterol lowering, a decrease in the risk of venous thromboembolism, reduction in the incidence of open-angle glaucoma as well as decrease in incidence of vascular events and mortality in the subset of CKD patients not receiving dialysis.

## Controversies and Concerns of Statin Therapy

Statins are generally well tolerated but one of the major concerns is the risk of adverse effects such as myopathy, hepatotoxicity, cognitive impairment and cancer. However, large meta-analyses and systemic reviews have failed to show conclusive evidence of cognitive impairment or risk of cancer with statin use.[38]

More recently, statin therapy has been linked to an increased risk of development of type II diabetes mellitus. The factors associated with new onset diabetes mellitus while on statins include elevation of baseline glucose, body mass index, hypertension and elevation of fasting triglycerides.[39]

Several studies such as the recent analysis from the JUPITER primary prevention trial showed that the cardiovascular and mortality benefit of statins was greater than the risk of developing diabetes, including those at high risk for developing diabetes.[40] For individuals with no risk factors for diabetes, statin therapy resulted in a 52% reduction in the risk of primary endpoint (MI, stroke, admission for unstable angina, arterial revascularization or cardiovascular death) ($p=0.0001$), 22% reduction in total mortality ($p=0.08$) and no increase in incidence of diabetes. In this population, 86 vascular events or deaths were avoided without any new cases of diabetes diagnosed. For individuals with one or more risk factors for diabetes (metabolic syndrome, impaired fasting glucose, body mass index $\geq 30$ kg/m$^2$, glycated hemoglobin $A_{1c}$ ($HbA_{1c}$) $>$ 6%) statin therapy was associated with a 39% reduction in primary endpoint ($p=0.0001$), 17% reduction in total mortality ($p=0.15$) and 28% increase in diabetes ($p=0.01$). These individuals had 134 fewer vascular events or deaths with 54 new cases of diabetes diagnosed. This analysis showed that the small risk of developing diabetes with statin therapy was limited to the group that was already at high risk– those with impaired fasting glucose, metabolic syndrome, elevated $HbA_{1c}$ and obesity.[40] Even with this increased risk, the overall benefit of statin therapy exceeded the hazard of diabetes in all participants. In a separate report, Jukema et al. also concluded that a 25 to 45% reduction in cardiovascular events with statin therapy outweigh the small increase in risk of developing diabetes.[38]

## Conclusion

The development of CVD is a lifelong process which can be favorably influenced by the use of statins in primary prevention. The current guidelines use cardiac risk scores to decide on the initiation of therapy. Despite the attractiveness of these prediction models there are clear limitations to this approach. The data presented here support the benefits of statins in patients with "normal" LDL-C as well as those at low risk by the risk score models.

Since age is such a powerful risk factor it would simplify the strategy to merely use one's degree of seniority as the point to initiate statins for primary prevention given the fact that the risk scores can be

problematic. As Yogi Berra said, "It's hard to make predictions, especially about the future."

Although proper diet and exercise are fundamental aspects of maintaining good cardiovascular health, they are not sufficient. The availability of generic statins makes it cost-effective to expand the use of statin therapy for primary prevention of cardiovascular disease. We believe the data presented here show that the immense burden of cardiovascular disease in the United States can be reduced by starting almost everyone over the age of 50 on statin therapy.

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## Disclosure

None reported.

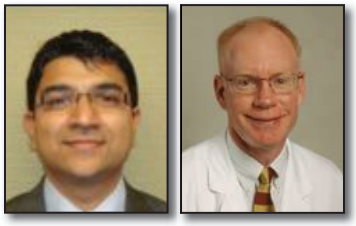
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# Almost Everyone Over 50 Should be Put on a Statin to Reduce the Risk of Cardiovascular Disease: *A Contrarian View*

*by Mayank Mittal, MD & William P. Fay, MD*

***Analysis of eleven statin trials involving 60,000 patients who were free of known cardiovascular disease did not find a significant reduction in all-cause mortality in statin-treated patients vs. controls. For low-risk adults, statin therapy is probably not necessary, nor cost-effective.***



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## Abstract

**3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, or statins, are a mainstay in the treatment of patients with established coronary artery disease (CAD) because of their proven efficacy in reducing cardiovascular death, myocardial infarction, and coronary revascularization procedures in this patient population. Statin therapy has also proven successful in the primary prevention of CAD. However, the absolute reduction in cardiovascular events is lower in primary prevention than in secondary prevention trials, and many of the primary prevention trials enrolled a significant number of patients with established cardiovascular disease and/or other high-risk features, such as diabetes mellitus. For these reasons we do not recommend widespread treatment of the general adult population with a statin. Rather, we advocate a strategy which involves collection of standard clinical data and the use of validated risk-prediction tools to stratify patient risk and limit initiation of a statin to those who are more likely to benefit from such therapy.**

## Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the United States and worldwide. 3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, or statins, are a mainstay in the treatment of patients with established CAD because of their proven efficacy in reducing cardiovascular death, myocardial infarction, and coronary revascularization procedures in this patient population. Several studies have examined the efficacy of statins in the primary prevention of cardiovascular events and death

in individuals without established CAD. As a whole, these studies revealed that statins also provide a beneficial effect in this population. These results beg the question "should most individuals >50-years old be treated with a statin to reduce the risk of developing CAD later in life, even if they are in good health and do not have hyperlipidemia?" Our reply to this intriguing and complex question is "no".

First, let's briefly review the data. Several studies examined the role of statins in the primary prevention of CAD. The drugs studied included pravastatin,[1-4] lovastatin,[5] atorvastatin,[6,7] and rosuvastatin[8]. The landmark WOSCOPS trial was the first to show positive results for primary prevention of CAD.[1] Subsequently, the AFCAPS/TexCAPS[5] and JUPITER[8] trials also showed significant reduction in major adverse cardiovascular events, including mortality. These trials were stopped prematurely because significant reductions in primary composite outcomes were observed.[5,6,8]

As a whole, the available data suggest that moderate-intensity statin therapy lowers the risk of nonfatal myocardial infarction and CAD-related death by approximately 20-30% without increasing non-cardiovascular death. The clinical investigators who conducted these trials are to be commended for their landmark work. However, great caution must be taken before extending statin therapy, as tested in published trials, into the general population.

It is important to realize that some of the primary prevention trials contained a significant incidence of individuals with established atherosclerotic cardiovascular disease or other high-risk cardiovascular features, such as diabetes mellitus, peripheral artery disease, or positive family history of CAD. For example, in the ASCOT-LLA Trial all patients had hypertension and approximately 10% had history of stroke or transient ischemic attack (TIA) at the time of enrollment. Exclusion of patients with diabetes mellitus, established atherosclerosis, and other CAD risk factors from primary prevention trials certainly would have decreased the number of cardiovascular events, and hence lessened the absolute benefit of statin therapy on cardiovascular endpoints. In fact, a meta-analysis of 11 statin trials involving >60,000 patients who were free of known cardiovascular disease at enrollment did not find a significant reduction in all-cause mortality in statin-treated patients vs. controls.[9] For low-risk adults, statin therapy is probably not necessary, nor cost-effective.[10]

While statin therapy has been shown to reduce cardiovascular risk by 20-30% regardless of baseline cholesterol profile, for an individual patient the predicted absolute benefit of statin therapy depends on his/her cardiovascular risk profile—i.e. patients with low-risk profiles will tend to derive lesser absolute benefit from statin therapy than patients with high-risk profiles.

For example, based on Framingham Heart Study data, a 45-year old non-smoking woman who is not taking antihypertensive medications, has no known cardiovascular disease, and has total cholesterol of 210 mg/dL, HDL cholesterol of 40, and systolic blood pressure 130 mmHg has a predicted 10-year risk of developing CAD of 1.0%. Moderate-intensity daily statin therapy would be anticipated to reduce this risk to approximately 0.75%--i.e. an absolute risk reduction of 0.25%. Do the cost, hassle, and potential side-effects of long-term statin therapy justify this degree of absolute risk reduction? Many individuals would answer "no" to this question. Conversely, a non-smoking 55 year-old man with drug-treated hypertension who has total cholesterol of 250 mg/dL, an HDL cholesterol of 30 mg/dL, and a systolic blood pressure of 150 mmHg has a predicted 10-year risk of developing cardiovascular disease of 21%. Statin therapy would be anticipated to reduce this individual's risk to approximately 15%, i.e. an absolute risk reduction of 6%. For this individual primary preventive therapy with a statin would appear to be much more reasonable, both from the patient's and physician's perspective.

Recently, 10-year risk prediction models have been questioned as adequate guides for initiation of statin therapy.[11] This is because for many young adults with active atherosclerosis risk factors the predicted incidence of developing clinically-manifest CAD within 10 years is <10% (i.e. below the threshold of initiating statin therapy), yet their lifetime risk of developing atherosclerotic cardiovascular disease may be quite high, often exceeding 50%.

However, individuals with low lifetime risk of ischemic heart disease can be identified. For example, Framingham Heart Study data suggest that individuals who reach age 50 years and have optimal cardiovascular risk factors (defined as total cholesterol <180 mg/dL, blood

pressure <120/80, non-smoker, and non-diabetic) have a low lifetime risk of developing cardiovascular disease (5.2% for men, 8.2% for women).[12] It would seem unwarranted in such individuals to initiate what could amount to several decades of statin therapy.

In terms of lowering risk of developing cardiovascular disease, it is also important to note that medical therapy (i.e. pills) is not the only option. A recent clinical trial involving >7000 individuals showed that dietary intervention can reduce the risk of developing cardiovascular disease.[13] In this study, which involved patients with diabetes mellitus or at least 3 other cardiovascular risk factors, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events over a follow-up period of several years (median 4.8) by approximately 30% compared to a control diet, which involved avoidance of dietary fat. Hence, dietary modification may achieve a relative benefit in primary cardiovascular disease prevention similar to that of moderate-intensity statin therapy. These results suggest that a preferred initial strategy to reduce cardiovascular risk for many individuals should be dietary and other lifestyle modifications (particularly physical activity), as opposed to statin therapy. While we all know that long-term adherence to dietary and lifestyle modification will be suboptimal for many individuals, adherence to long-term primary prevention oral medications has also been problematic.[14]

## Conclusion

In conclusion, we do not advocate routine administration of statins to healthy adults to reduce the risk of developing CAD. This recommendation parallels the approach advocated for patients with atrial fibrillation. While oral anticoagulant drugs significantly reduce the risk of developing a first stroke in patients with non-valvular atrial fibrillation, current guidelines do not advocate that all patients with atrial fibrillation be treated with warfarin or another oral anticoagulant drug. This is because low-risk patients can be identified by easily applied risk-prediction tools, such as the $CHADS_2$ score. In low-stroke-risk patients long-term oral anticoagulant therapy is not justified. Similarly, for the primary prevention of CAD we advocate a quantitative strategy that is based upon office-based history and physical examination, fasting lipid profile data, and use of simple risk-prediction tools, such as the Framingham Heart Study risk calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp). With this readily retrievable, low-cost information the health care provider and patient can discuss the potential benefits of statin therapy (as well as other pharmacological and non-pharmacological interventions) and decide together how to proceed.

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## Disclosure

None reported.



# Will Routine Use of Statins After Age 50 Become as Common as Fluoridating Drinking Water? It Should!

*by Jerry Kennett, MD*

**As usual, this boils down to the most important issue in all medical decision-making "Does the benefit outweigh the risk?"**



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In 1945 Grand Rapids, Michigan initiated the first community water fluoridation project designed to prevent tooth decay in children less than 8 years of age. By 2006, the Center for Disease Control reports 69.2% of United States residents on public water systems are receiving fluoridated water.[1] How does that relate to statins; well please read on. In this issue of *Missouri Medicine* Drs. Fay and Mittal, writing as antagonist (CON), and Dr. Bogart along with medical student Sandesara, as protagonist (Pro), debate the important issue of whether almost everyone over age 50 should preventively be on a statin medication. Both make excellent points and do a good job of reviewing the literature related to statin therapy.

As usual, this boils down to the most important issue in all medical decision-making "Does the benefit outweigh the risk?" The overwhelming evidence is statin therapy in patients with coronary artery disease or coronary artery equivalent, which includes patients with diabetes, symptomatic carotid artery disease, peripheral vascular disease, abdominal aortic aneurysm, and even those with chronic kidney disease, leads to a significant reduction in cardiovascular events including nonfatal myocardial infarction, coronary death, stroke, and even all-cause mortality.[2]

The question then becomes, what about those individuals with a 10-year risk of developing coronary heart disease of less than 20%. The Cholesterol Treatment Trialists (CTT) Collaborators have now published two meta-analyses of the effects of lowering LDL cholesterol with statin therapy in individuals at low risk of vascular disease. Their analyses showed that statin reduction of LDL cholesterol of 1 mmol/L of LDL cholesterol reduced the risk of major vascular events irrespective of age, sex, baseline LDL cholesterol, or previous vascular disease by approximately 20% over a period of 5 years. The analyses also showed that further reduction in LDL cholesterol obtained by more intensive statin regimens led to further reduction in the instance of major coronary events, coronary revascularizations, and ischemic stroke.[3, 4]

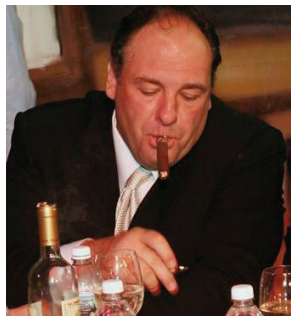
So, if statins are that beneficial what about the risk of harm? The most common adverse side effects of statins are myopathy and extremely rarely rhabdomyolysis. Discontinuation or reduction of the dose usually leads

## *A Killer of a Lifestyle*

*by John C. Hagan III, MD*

# Gandofini Failed to Take "Preventative Cardiology" Tips to Heart

Actor James Gandofini, age 51, died of a massive myocardial infarct June 19, 2013, in Italy. His demise has brought "sudden death" due to heart disease to the public's attention.



For the past two years *Missouri Medicine* has published the acclaimed series "Preventive Cardiology." If seeking an example of what "not to do" to prevent heart disease, one could hardly find a better person than Gandofini, best known for his portrayal of "Big Tony" in the award winning series "The Sopranos."

According to *The New York Post* quoting restaurant sources, Gandofini's last meal consisted of four shots of rum, two beers, two orders of large fried king prawns slathered in mayonnaise chili sauce and a huge portion of foie gras. A meal of this magnitude was not unusual for the obese actor and usually left his serving bowls and plate empty. His cardiac risk factors easily identified include obesity, lack of exercise, tobacco abuse, atherogenic diet, heavy alcohol use (he had attended alcohol anonymous in the past), and a stressful lifestyle (he was engaged in a legal battle with ex-wife and had anger management problems that included punching himself for fluffing a line during filming). While it is likely there were also problems with hypertension, lipid elevations, and possibly diabetes, these could not be confirmed.

In reviewing newspaper and internet articles, it is frankly shocking to find descriptions of Gandofini as looking "healthy" before his death and that the autopsy-proven fatal myocardial infarct was "death by natural causes." His persona, lifestyle, and photos had an egregiously unhealthy motif. What is natural about dying almost 29 years before life expectancy tables indicate say you should? As we wind down our Preventive Cardiology series let us not forget that cardio-vascular disease is the number one cause of death in the USA with over 600,000 deaths and over 715,000 myocardial infarcts annually. Gandofini was the anthesis of a heart healthy lifestyle. Let us carry the "preventive cardiology" message and heart healthy diet and lifestyle to our patients each and every visit.

to resolution of these symptoms. The primary sources of concern about long-term complications from statin therapy have been: a possible adverse effect on cognition, a causative role in cancer, and predisposition to diabetes.

In a recent review entitled "The Controversies of Statin Therapy", Cannon and associates report that based on two large randomized controlled trials, as well as 12 other smaller controlled trials, there is no evidence to conclude statins have detrimental or beneficial effects on cognitive function.[5]

There is now exciting new study data on the Danish population which shows a 15% reduction in all-cause mortality and cancer specific mortality in statin users as compared to nonusers in patients with cancer. This included the four most common cancers – lung, prostate, breast, and colorectal.[6] Cannon's review showed no evidence statins actually cause cancer.[5]

Lastly, we turn our attention to diabetes mellitus. There is evidence of an approximately 10% increased risk of type II diabetes mellitus in individuals taking statin drugs. This is most common in individuals who have other predispositions to diabetes. However, in the same studies that show an increased incidence of diabetes there is an overall benefit with statin therapy due to a significant reduction in coronary heart disease, death, myocardial infarction, and stroke. These major reductions of cardiovascular events of patients on statins outweighs the small absolute risk of diabetes.[7]

In conclusion, we are not at the point of adding statins to our drinking water as we did fluorides. I agree with the protagonists that in most individuals attainment of age 50 alone is enough of a risk factor to strongly consider statin therapy.

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## Disclosure

None reported.

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# Eye On Statins: A Comprehensive Review

*by Evan A. Olson, MD, Dean P. Hainsworth, MD, Geetha Davis, MD & John C. Hagan, III, MD*

**As cholesterols are prevalent throughout the entire body, statins can potentially have beneficial and/or destructive effects on a range of tissues, including the brain and eyes.**



Evan A. Olson, MD, (above) Dean P. Hainsworth, MD, and Geetha Davis, MD, MSMA member since 2010, are with the Mason Eye Institute at the University of Missouri. John C. Hagan, III, MD, is with Discover Vision in Kansas City, Missouri.
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## Abstract

**Over the last 25 years, statins have demonstrated their safety from an ophthalmologic standpoint. Studies relating statin to cataract formation are insufficient to alter the usual and customary prescription of statins. If there is an association between statins and cataracts, it is weak and clinically insignificant. Prospective studies have not demonstrated a benefit of adding statin therapy in patients with age-related macular degeneration (ARMD), but these studies have not been adequately powered to detect moderate differences. A subset of patients with persistently elevated lipids despite taking statins may be at higher risk of developing wet ARMD. The use of statins for the prevention and/or treatment of glaucoma patients warrants further prospective study. There is a possibility that statins may unmask or exacerbate myasthenia gravis.**

## Introduction

Since their introduction in 1987, statins have become ubiquitous in medicine. They have demonstrated a clear role in the secondary prevention of cardiovascular disease. They lead to a reduction in serum cholesterol levels by inhibiting hydroxymethylglutaryl-CoA reductase. As a general rule, statins are well-tolerated and have an excellent safety profile. The most well-documented side effects of statins include elevated liver enzymes, muscle aches and rhabdomyolysis in a minority of patients.[1] As cholesterols are prevalent throughout the entire body, statins can potentially have beneficial and/or destructive effects on a range of tissues, including the brain and eyes. The FDA recently included a warning that statin has been associated with cognitive decline.[1] This has led to vigorous debate among physicians with regard to whether or not this warning is warranted and if so, whether it should change clinical practice patterns.

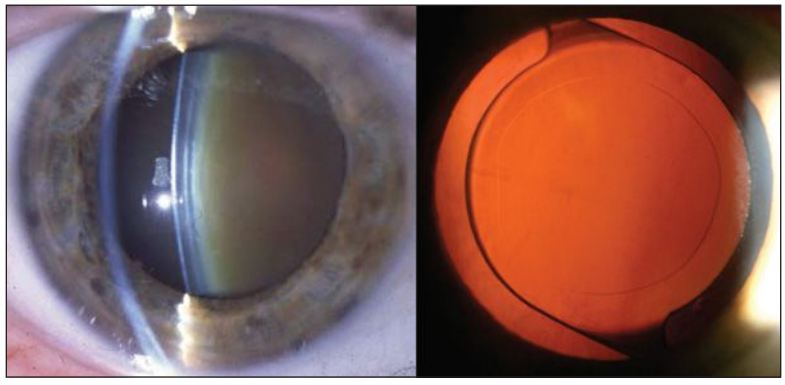
There is also controversy with regard to the potential effects of statins on the eyes. As early as 1987, some physicians recommended baseline eye exams prior to the initiation of statin therapy because of a possible correlation with cataracts.[2] This was not an uncommon cause for ophthalmic referrals in the late 1980s and early 1990s. Since then, more than 30 peer-reviewed articles have addressed the connection between statins and cataracts with conflicting results. More than 20 articles have addressed a potential connection between statins and age-related macular degeneration (ARMD). The earliest of these studies reported a strong protective effect of statins against ARMD; subsequent larger studies have failed to demonstrate any benefit in preventing or slowing ARMD. Over a dozen publications have addressed the connection

between statin therapy and glaucoma progression. The majority of these studies have concluded that patients on statins are less likely to have glaucoma progression than non-users. In this paper we review and summarize the relevant literature for physicians prescribing statins and/or monitoring for associated ocular side effects.

## Cataracts

Worldwide, cataracts are the leading cause of reversible blindness and visual impairment (defined as 20/40 or worse vision in the better eye).[3] In industrialized countries with access to ophthalmologists, cataracts are still a major cause of visual impairment (See Figure 1). Cataract surgery with insertion of an intra-ocular lens (IOL) is one of the most common operations in developed countries and as a result, cataract-induced blindness is rare in the U.S. Surgical treatment of cataracts can eliminate vision loss due to the opaque human lens. Several risk factors have been clearly linked to accelerated cataract formation including diabetes, smoking, and ultraviolet (UV) exposure.[4] Several medications are associated with iatrogenic development of cataracts. Decades of research has shown a consistent causative connection between cataracts and the long-term use of oral steroids.[5] Topical steroid eye drops and inhaled steroids have also been implicated. Some antipsychotics (chlorpromazine in particular) frequently cause opacifications of the lens.[6] However, a causative relationship between statins and cataracts has not been conclusively established. Several large studies have been published with conflicting results. Some have suggested a protective effect while others find statin users at increased risk for cataract formation.[2,7-10,12]

***Figure 1***
Age-related nuclear sclerotic cataract compared to a patient who has undergone cataract extraction with placement of an artificial intraocular lens.



The Blue Mountains Eye Study reported a 50% reduction in the risk of cataract development in a population of about 2,000 elderly statin users who were followed for 10 years.[7] In the Beaver Dam Eye Study, more than 1,000 patients had gradable lens photographs and were deemed to be "at risk" of developing nuclear cataracts. After five years, 12% of statin users and 17% of nonusers went on to develop nuclear cataracts (the most common type of age-related cataract).[8] Persistent statin use was significantly associated with a reduced risk of cataract in a retrospective cohort of more than 180,000 new statin users in a large health organization in Israel.[9] Interestingly, the difference was only significant in those under 75 years of age. When the ophthalmic records of more than 48,000 patients within the Kaiser database were reviewed,[10] statin use was present in 64% of patients undergoing cataract surgery compared to only 56% of controls. In patients younger than 65, statin use for greater than five years was associated with the lowest risk of cataract surgery.

Although each of these four large studies reported a protective effect of statins on cataracts, the results may reflect patient lifestyle more than an intrinsic statin pharmacologic effect. The "healthy user bias" is the presumption that patients who are adherent and persistent with medication schedules are also more likely to engage in healthy lifestyle habits (not smoking or abusing alcohol for instance) and follow-up with their physicians. The healthy user effect has demonstrated that statin users enjoy benefits that are unrelated to their use. As an example, statin users practice better dental hygiene, have less drug dependency, and fewer workplace and automobile accidents.[11] It is possible that a decrease in the incidence of cataracts is a "halo" bias in these healthy users.

Not all studies have demonstrated a protective effect of statins with regard to cataracts. The University of Waterloo School of Optometry in 2012 reported an earlier age of cataract development in statin users compared to nonusers.[12] In their non-diabetic population, half of statin users had a cataract by age 55 compared to age 57 in statin non-users. In their diabetic population, half of statin users had a cataract by age 52 compared to age 55 in statin non-users. There are several limitations of this study: it involved much fewer patients than the Kaiser review (n=6397);

it did not take into consideration the duration of statin therapy; and it did not state whether the cataracts were visually significant requiring surgery.

While statistically significant, this study is not clinically relevant. Even if statin users developed cataracts ten years sooner than their counterparts, it wouldn't trump statins well-established benefits in the prevention/treatment of cardiovascular disease and related mortality. Hyperbolic and semi-hysteric media coverage of these and similar findings can unnecessarily frighten patients and may lead to non-compliance with life-saving statin medications.

To our knowledge, there has been no randomized controlled trial which has demonstrated any significant connection between statins and cataracts. Physicians should continue prescribing statins when they are medically indicated without worrying about an association with cataracts.

## Age-Related Macular Degeneration

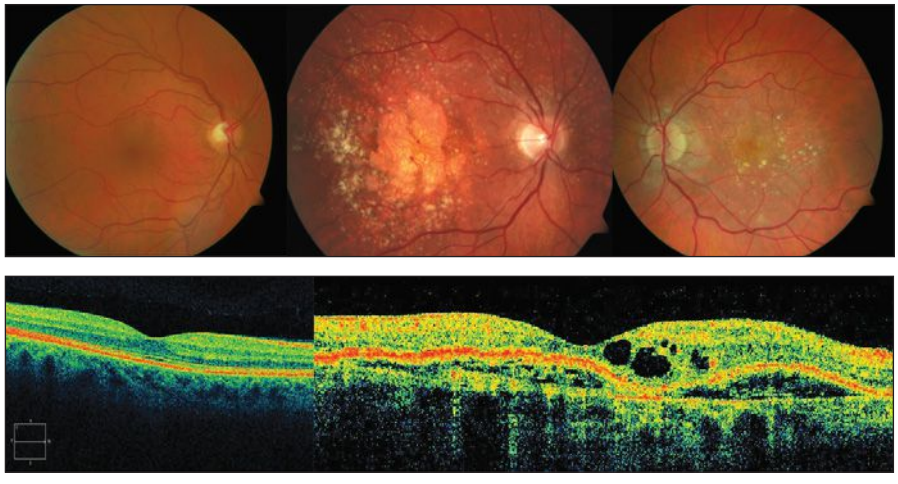
More than one million people in the United States age 40 and older are legally blind. The most accepted definition of "legal blindness" is a best corrected visual acuity of 20/200 or worse or a visual field of less than 20 degrees in the widest diameter in the better eye. The most common cause of legal blindness in working age American adults is diabetic retinopathy. After age 65, the leading cause of legal blindness is ARMD.[13] There are two forms of ARMD: non-exudative or "dry" (90% of cases) and the neovascular or exudative "wet" form of ARMD (10% of cases). Although less common, the wet form causes 90% of the legal blindness associated with AMRD. Wet ARMD is felt to develop from pre-existing dry ARMD. Although there has been remarkable progress in the treatment of wet ARMD, there are many treatment-resistant cases which cause impaired vision and legal blindness. As a result, great attention has been directed toward the prevention of dry ARMD and its conversion into wet ARMD (See Figure 2).

The earliest clinical hallmark of dry ARMD is the presence of numerous drusen within the macula of the retina. These are tiny yellow or white collections of extracellular debris that build up in between the retinal pigment epithelium (RPE) and Bruch's membrane. These deposits are lipid-rich; it seems intuitive that there would be a beneficial role for lipid-modifying agents in treating or preventing ARMD. The risk factors associated with ARMD are also very similar to the risk factors for atherosclerosis. This gives further strength to the hypothesis that the treatment of atherosclerosis will have beneficial effects in ARMD patients.

With this hypothesis in mind, a national insurance claims database of over 100,000 patients was reviewed for the years from 2001 to 2007.[14] About half of the beneficiaries were on statins. During the study time-frame, there were almost 5,000 incident cases of dry ARMD and about 800 incident cases of wet ARMD. The results of this study were unexpected. Patients with elevated lipid levels and more than one year of statin use had a higher hazard ratio for the development of wet ARMD. The fact that this was only significant in patients with persistently elevated lipid levels may indicate that there is a subset of patients who, despite being prescribed statins, continue to have elevated cholesterol levels which increases their risk of developing wet ARMD. Based on a number of limitations in study design, the authors concluded that there was no rationale for making changes in the use of statins to treat dyslipidemias based on their findings.[14]

A Cochrane Review was published in 2012 on the potential of statins to treat ARMD.[15] Unfortunately, there were only two randomized controlled trials that met the selection criteria for inclusion in their analysis. The first trial involved 30 subjects and compared 20 mg of simvastatin to a daily placebo for a period of three months. No differences were observed after three months of therapy or 45 days after the completion of treatment. Only a profound effect

***Figure 2***
Fundus photos of a normal macula, severe dry macular degeneration and wet macular degeneration, respectively. Below, Optical Coherence Tomography (OCT) demonstrates a normal macula compared to a macula with exudative (wet) AMD.



would be expected to be picked up with such small numbers and short follow-up period. The second study is an ongoing trial entitled, "The Age-related Maculopathy Statin Study."[16] This is a three-year prospective, randomized, controlled trial comparing 40 mg of simvastatin to a daily placebo in patients at high risk of ARMD progression. A preliminary analysis of data from 42 enrolled patients has not demonstrated a clear benefit at 12 months of follow-up. Unless larger and/or longer studies demonstrate a clear benefit, there is insufficient data for statins to be included in dry ARMD prevention and treatment even in high-risk patients.

## Glaucoma

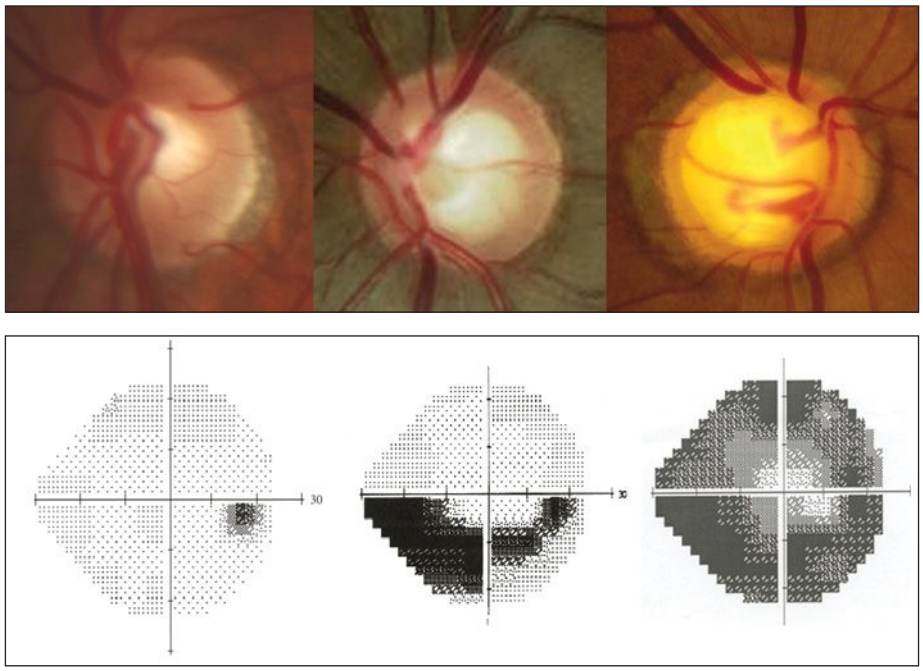
If statins do play a protective role in the eye disease it may be in patients with open angle glaucoma (OAG). Recent studies[18, 21] suggest that statins may halt insidious, painless and progressive loss of peripheral vision due to glaucoma (See Figure 3). It is estimated that nearly three million Americans have glaucom.[17] In open-angle glaucoma (OAG), the most common form of glaucoma, there are virtually no symptoms. Consequently, about half of cases remain undiagnosed.[13] Unlike cataracts, the visual loss associated with glaucoma is generally irreversible. Recognition and treatment of glaucoma in the beginning stages is essential to limit visual impairment. The most identifiable risk factor for glaucoma is elevated intraocular pressure (IOP) with diurnal variations that are often in the normotensive range. Current treatment strategies use medicines, lasers and/or surgeries to lower the IOP to non-damaging levels (which often vary from patient to patient). Other than lowering the IOP, there aren't other well-established methods for treating glaucoma. If another mechanism for treating glaucoma could be discovered, it would represent a huge breakthrough in the treatment of a disease that can severely limit ones quality of life.

Several recent studies have demonstrated that statin users are less likely to develop OAG. In 500,000 patients with hyperlipidemia, those who took statins continuously for at least two years had an 8% decreased risk of developing glaucoma and a 9% decreased risk of progressing from glaucoma suspect to a definitive diagnosis of OAG.[18] There are several biochemical, mechanical, and vascular theories to explain why the optic nerve slowly dies in open angle glaucoma. The protective effect of statins may be a result of their regulation of nitric oxide synthase, which increases blood flow to the retina and optic nerve.[19] There is an increasing body of knowledge which supports that statins may inhibit apoptosis in the central nervous system.[20] Either of these mechanisms could inhibit glaucomatous damage. Whatever the mechanism, the sentinel finding of a putative statin neuroprotective effect is unique as it has been shown to be independent of any change in IOP.[21] Opening up another avenue in the treatment of glaucoma would represent a profound advancement in disease management. Several prospective randomized studies have been planned to further investigate the role of statins in the prevention and/or halting of glaucoma.

## Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune condition characterized by muscle weakness due to impaired transmission at the neuromuscular junction. From an ocular standpoint, myasthenic weakness can lead to ptosis,

***Figure 3***
Normal optic disc appearance compared to moderate and severe glaucomatous cupping, respectively. Normal visual field with physiology blind spot compared to moderate and severe glaucomatous visual field loss, respectively.



diplopia and ophthalmoplegia. Dozens of medications have been reported to unmask or worsen MG.[22] In 2000, the first case report of statin-induced MG was published.[23] Subsequently additional case reports suggest an association between the two.[24-28] The mechanism underlying this association is not clearly understood but several theories have been proposed. Statins have been shown to inhibit B-lymphocyte activation and MHC class II antigen presentation[29-30] which could predispose to developing MG. It is also possible that a MG patient's weakness can simply be exacerbated by statin-induced myopathy.

It is not definite that patients with MG should be discontinued from using statins. However, they should be informed about the possibility of statins being associated with MG. If a new statin-user develops myasthenic weakness within the first several months of use, the statin should be discontinued.

## Summary

Over the last 25 years, statins have demonstrated their safety from an ophthalmologic standpoint. Studies relating statin to cataract formation are insufficient to alter the usual and customary prescription of statins. If there is an association between statins and cataracts, it is weak and clinically insignificant. Prospective studies have not demonstrated a benefit of adding statin therapy in ARMD patients, but these studies have not been adequately powered to detect moderate differences. A subset of patients with persistently elevated lipids despite taking statins may be at higher risk of developing wet ARMD. The use of statins for the prevention and/or treatment of glaucoma patients warrants further prospective study. There is a possibility that statins may unmask or exacerbate myasthenia gravis.

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## Disclosure

None reported.

MM



# Red Yeast Rice for Dyslipidemia

*by Shariq Shamim, MD, Firas J. Al Badarin, MD, James J. DiNicolantonio, PharmD, Carl J. Lavie, MD & James H. O'Keefe, MD*

**Red yeast rice use should be reserved for patients who are intolerant to or unwilling to try statins, with the understanding that its long-term benefit and safety are not firmly documented yet.**



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## Abstract

**Red yeast rice is an ancient Chinese food product that contains monacolins, chemical substances that are similar to statins in their mechanisms of action and lipid lowering properties. Several studies have found red yeast rice to be moderately effective at improving the lipid profile, particularly for lowering the low-density lipoprotein cholesterol levels. One large randomized controlled study from China found that red yeast rice significantly improved risk of major adverse cardiovascular events and overall survival in patients following myocardial infarction. Thus, red yeast rice is a potentially useful over-the-counter cholesterol-lowering agent. However, many red yeast rice formulations are non-standardized and unregulated food supplements, and there is a need for further research and regulation of production.**

## Introduction

Whereas statins are effective in lowering low density lipoprotein-cholesterol (LDL-C) and improving prognosis in patients with or at risk for cardiovascular (CV) disease, statin-induced myalgia is a common complaint, with an incidence of approximately 10-11%, often leading to medication non-adherence or discontinuation.[1] This has sparked interest, especially among the general public, for over-the-counter nutraceutical products with comparable efficacy and improved tolerability that might be used for patients who are statin-intolerant or unwilling to take one of the prescription agents from this important class of medications.

Red Yeast Rice (RYR) is one of the non-prescription supplements used for treatment of dyslipidemia, which has gained special attention recently. This agent, also known as *"Red Koji"* or *"Hong Qu,"* is an ancient natural product that has been extensively used in China for many centuries.[2] RYR is prepared by fermenting strains of the fungus *Monascus purpureus* on moist rice, and hence it derives its name from the red coloration the fungus imparts to the rice upon which it is grown. RYR has traditionally been used to make rice wine, as a food color or flavor enhancer and as a non-prescription herbal therapy traditionally prescribed for digestive

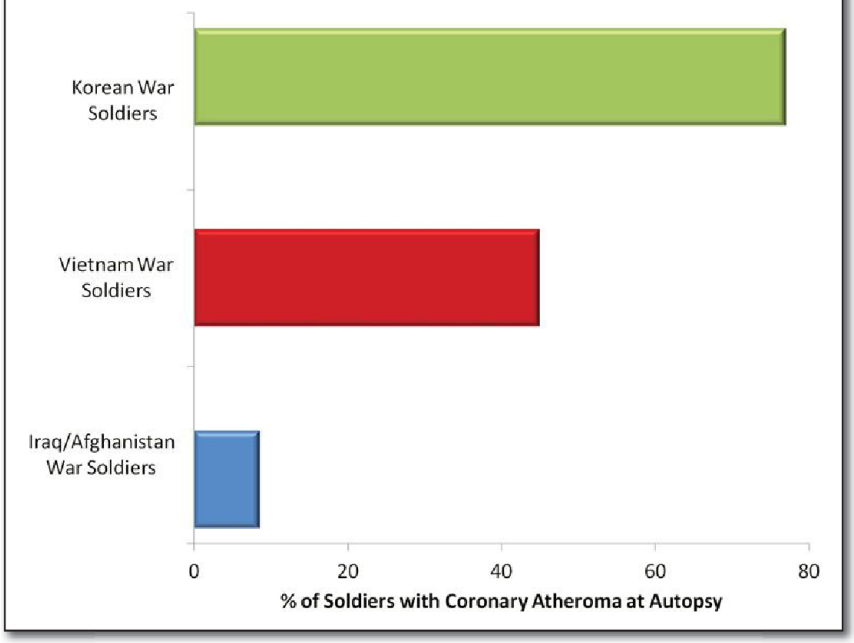
and circulatory disorders and in recent years, for treatment of dyslipidemia.[2, 3]

Over the last half century the prevalence of atherosclerosis in the general United States (U.S.) population has fallen dramatically (See Figure 1).[4] In 1979 a Japanese scientist isolated a compound initially named monacolin K from a *Monascus* fungus culture. This natural byproduct was subsequently renamed lovastatin and was the seminal compound out of which grew the statin class of cholesterol-lowering medications—the most commercially successful therapeutic class in the history of the pharmaceutical industry.[5] RYR is typically 0.4% monacolins, of which the majority will be monacolin K (identical to lovastatin). However, the cholesterol-lowering properties of RYR are attributable not only to the naturally-occurring HMG CoA reductase inhibitor activity of monacolins but also to the mono-unsaturated fatty acids and phytosterols contained in these products.[2, 3, 5, 6] The RYR dose commonly used in clinical trials is 1,200 to 4,800 mg/day containing roughly 5 to 20 mg total monacolins. Studies have consistently reported that RYR effectively lowers LDL-C with generally good patient tolerability.[7] Consequently, RYR use has become very common among patients unwilling to use statins or those with statin-induced myalgias, with an estimated $20 million spent on RYR-containing supplements in the year 2008.[8]

Notwithstanding this popularity, a number of controversies about the use of RYR currently exist and several questions about the role of RYR in the treatment of dyslipidemia remain unanswered. For example, the fact that RYR preparations contain variable and undisclosed amounts of lovastatin creates confusion about whether RYR should be marketed as an over-the-counter supplement or should be regulated as prescription medicine. In addition, of the ideal dose of RYR that can achieve safe and effective reduction of LDL-C is somewhat uncertain due to the variable monacolin content of the different formulations. Also, there is lack of consistency in the composition of RYR in the absence of tight regulatory guidelines on the production of RYR. Some of the published studies evaluated RYR preparations that are available only in China. However, several RYR products are manufactured in the U.S. and well-designed studies evaluating their LDL-C lowering efficacy have been published. Still, the single large scale study powered to assess the effect of RYR on clinical endpoints (including death, myocardial infarction [MI], etc.) was performed in China using a RYR manufactured there.

In this review, we aim to shed light on the existing literature regarding RYR and to explore some of the controversies around the role of RYR in contemporary practice. We will review what is known, what is unknown and what is uncertain about the role of RYR as a lipid-lowering supplement in patients unwilling or unable to take statins.

***Figure 1***
Coronary atherosclerosis prevalence at autopsy of American soldiers has fallen dramatically over the last five decades despite similar mean ages (about mid-20s) for all three cohorts.[4]




## RYR is Effective for Treatment of Elevated Cholesterol

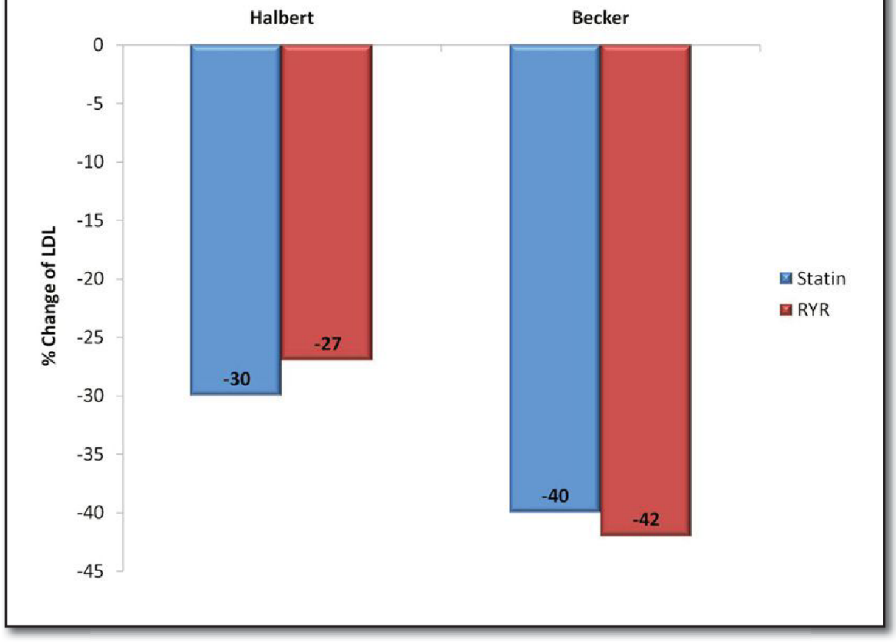
Several studies have demonstrated the efficacy of RYR as a lipid-lowering agent.[3, 6, 7, 9, 10] Overall, the use of RYR resulted in a 21 to 32% reductions in LDL-C,[3, 6, 7, 9, 10] 13 to 44% reductions in triglycerides(TGs)[3, 6, 7, 9, 10] but no

consistent effects on high density lipoprotein-cholesterol (HDL-C).[3, 6, 7] This effect on lipid parameters varied by the active component in RYR.[7] Cholestin and *Xuezhikang* were more effective in lowering LDL-C compared to *Zhibituo* (22%, 27 to 32% and 5%, respectively).[7] On the other hand, *Xuezhikang* and *Zhibituo* produced more pronounced reductions in TGs (6-44% and 27-38%, respectively) compared to Cholestin (7%).[7]

More recent studies using RYR manufactured in the U.S. with more rigorous scientific methodology have also demonstrated the efficacy of RYR. Halbert et al. showed comparable reduction in LDL-C with RYR (2,400 mg twice daily) and pravastatin (20 mg twice daily) over a 12-week period, (30% and 27%, respectively).[11] Similarly, Becker et al. demonstrated that RYR (1,800 mg twice daily) in combination with fish oil and therapeutic lifestyle changes significantly decreased total cholesterol (32%) and LDL-C (42%) to the same extent seen in the control arm of the study treated with simvastatin 40 mg (27% and 40%, respectively)[12] (See Figure 2). With a significant reduction in weight in the study group (a mean difference of 4.4 kg) compared to the control group, it remains hard to determine the relative contribution of RYR to the results compared to other lifestyle changes or fish oil.[12] Of interest, taking RYR containing the equivalent of about 10 mg of lovastatin per day results in LDL-C reduction similar to that produced by 20-40 mg of lovastatin daily.[9] This may be due to other unknown mechanisms by which RYR helps in reducing LDL-C.[6, 13]

However, existing literature in this field has several limitations that need to be acknowledged. Many of the studies of RYR that were included in the largest meta-analysis were published in the Chinese literature. Moreover, they were of small size and limited by their technical quality. Furthermore, the RYR preparations used in some of these studies are not available elsewhere in the world, which might bring into question the relevance of this evidence to the use of RYR in the US. Therefore, rigorous studies of products manufactured according to the tight regulations are strongly warranted.

***Figure 2***
Effectiveness of RYR for lowering LDL-C in contemporary US clinical trials.[11, 12]



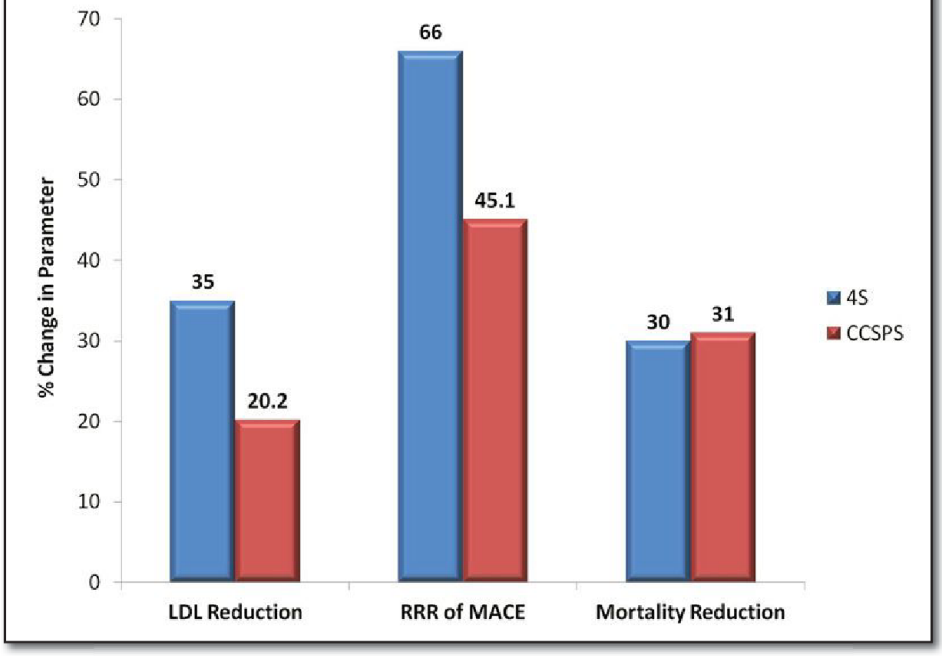

## RYR is Well-tolerated as a Supplement for Treatment of Dyslipidemia

Since the logical target population for statin alternatives, including RYR, is the group of individuals unable or unwilling to take statins, the safety and tolerability of RYR need to be well documented before it can be routinely recommended to this patient population. The reported incidence of statin intolerance among patient populations treated with prescription statins is estimated to be in the range of 2-15%.[1, 14-16] The rates of myalgias reported with RYR use among patients previously intolerant to statins are low (5%-7%).[8, 11] Halbert et al. reported no statistically significant difference in statin-induced myalgias among patients previously intolerant to statin who were treated with RYR compared to those re-challenged with pravastatin, with incidence of musculoskeletal complaints of 5% in RYR and 9% in pravastatin group ($P = 0.99$).[11] The reported recurrence rates of myalgias in patients re-challenged with a different prescription statin

ranges from 0% to 57%.[17-23] Therefore, the rates of statin-induced myalgias among statin intolerant patients treated with RYR appears to be low and acceptable.

RYR use has also been associated with adverse effects other than myalgias, including dizziness and loose stools, that have in some instances led to discontinuation of the RYR.[24] In addition, rhabdomyolysis has been reported in a renal transplant recipient on RYR and concomitant cyclosporine therapy.[25] Four cases of RYR-induced myopathy, manifested as myalgias with an increase in creatine kinase (CK) level without rhabdomyolysis have been reported, three of which resolved after withdrawal of therapy.[25] Additionally, reversible elevation of CK levels among individuals on RYR[26] and symptomatic hepatitis in a patient on RYR that resolved after cessation have been reported.[27]

***Figure 3***
Comparison of simvastatin in 4S versus RYR in CCSPS for improving LDL-C, relative risk reduction of major adverse cardiac events (RRR MACE) and mortality during these placebo-controlled trials. [15, 28]




## Impact of Treatment with RYR on Long-term Outcomes in Dyslipidemic Patients

Data on long-term effects of RYR on clinical endpoints are predominantly from the Chinese Coronary Secondary Prevention Study (CCSPS),[28] which was carried out over a four-year period and enrolled 4,870 patients with history of previous MI between 18-70 years of age. Patients were randomized to receive placebo or Xuezhiang (XZK), a purified commercial derivative of RYR available in China. The study reported a decrease in LDL-C and TGs of 20% and 15%, respectively and a 5% increase in HDL-C from baseline. Major changes were noted within 6-8 weeks of the initiation of therapy in the study, after which the values stabilized. This study reported a significant reduction in rates of major adverse CV events with XZK use compared to placebo (5.7% vs. 10.4%, respectively, $P < 0.001$)[28] (See Figure 3).

These results, although impressive, need to be interpreted in the context of the following limitations. First, the RYR preparation used in the study was manufactured in China, and the same composition might be difficult to reproduce in other parts of the world. Replication of this study using other RYR preparations in the US will be difficult from an ethical standpoint given the difficulties of withholding statins from patients with prior MI, a clinical therapy that has demonstrated unequivocal evidence for benefit particularly among individuals with documented coronary heart disease (CHD). Second, the CCSPS study enrolled patients whose LDL-C levels were in the lowest range and HDL-C levels in the highest range compared to other landmark secondary prevention trials, including the 4S, CARE, LIPID and PROVE-IT studies, all of which were performed in western populations (See Table 1).[15, 29-31] Whether the results will be applicable in other risk groups is unknown.

## The Effect of RYR on Other Markers of Atherosclerosis

In addition to their established role in improving overall CV prognosis in patients with or at-risk for CV disease, statins have been shown to exert a favorable

*Table 1*
Comparison of Baseline Serum Cholesterol Levels in Major Secondary Prevention Statin and RYR Trials

| Study | CCSPS[28] | 4S*[15] | CARE[31] | LIPID[30] | PROVE-IT[29] |
|---|---|---|---|---|---|
| **Agents** | RYR (Xuezhikang) vs Placebo | Simvastatin vs Placebo | Pravastatin vs Placebo | Pravastatin vs Placebo | Pravastatin 40 mg vs Atorvastatin 80 mg |
| **LDL-C** | 129 ± 28 | 188 ± 25 | 139 ± 15 | 150 ± 20 | 106 ± 20 |
| **HDL-C** | 46 ± 15 | 45 ± 11 | 39 ± 9 | 36 ± 5 | 39 ± 6 |
| **TC** | 207 ± 26 | 260 ± 26 | 209 ± 17 | 218 ± 22 | 154 ± 39 |

effect on novel risk factors and markers of subclinical atherosclerosis independent of their lipid-lowering action. There are limited data on the impact of RYR on these endpoints. The use of Xuezhikang resulted in a significant reduction in C-reactive protein (CRP), interleukin-6 and endothelin-1.[32] Another study done in China showed improvement in endothelial function with Xuezhikang measured with flow-mediated vasodilation after 6-weeks of treatment, along with improvement in high sensitivity-CRP.[33] Based on this limited body of literature, RYR may exert beneficial effects on inflammation and other markers of atherosclerosis, though more studies need to be performed.

## Should RYR be Considered as a Drug or a Food Supplement?

The controversy surrounding the marketing of RYR as a food supplement demonstrates the legal confusion between the categorization of a substance as a food or a drug. According to the Federal Drug Administration (FDA), a substance cannot be classified as a food supplement if it contains ingredients that are marketed as drugs; and if the supplement was introduced in the market after the introduction of the said drug. The use of Cholestin was banned by the FDA as a food supplement in the spring of 2001, since it contains naturally-occurring lovastatin.[27] The FDA, in effect, considers RYR to be an over-the-counter statin, and as such, an unapproved drug. However, RYR is available to the US population, on internet pharmacies and in most retail outlets where nutritional supplements are sold. RYR is often manufactured with unregulated methods and some samples from China have been found to contain contaminants such as citrinin, which is a nephrotoxic.[2, 3] Before being introduced as a drug in the market, RYR would be subject to the US FDA's policy of being registered as a new drug and consequently would have to undergo various clinical trials and studies. Due to the very high costs of such an endeavor, it is unlikely that any manufacturer will attempt to obtain FDA approval for RYR as a drug, particularly in light of the availability of atorvastatin, simvastatin, lovastatin, pravastatin and fluvastatin as inexpensive generic medications.[3]

## The Role of RYR in Management of the Statin Intolerant Patient

Statin-induced myalgia remains a clinical challenge for many patients and their physicians. Several treatment strategies exist, including decreasing the dose of statins, intermittent statin dosing, therapeutic lifestyle changes and non-statin pharmaco-therapies such as ezetimibe, niacin, fibrates or bile acid sequestrants.[34] Nevertheless, there will always remain a subset of patients who will not tolerate any statin and the use of nutraceuticals, such RYR, might play a role in conjunction with therapeutic lifestyle changes for these individuals.

## Conclusion

RYR, ideally used in doses of 1,200 to 4,800 mg/day in divided doses, is effective in lowering total and LDL-C in dyslipidemic patients and may be a potential alternative for patients who are statin-intolerant or do not wish to take a prescription lipid lowering agent. Nonetheless, the impact of its use on long-term prognosis in patients with known CHD is still somewhat uncertain. The existing literature is fraught

with limitations and additional well-designed studies using RYR preparations with standardized composition are needed. Currently, RYR use should be reserved for patients who are intolerant to or unwilling to try statins, with the understanding that its long-term benefit and safety are not firmly documented yet. If and when RYR is used, it should be a formulation manufactured by a company that documents the safety, purity and composition of its product. Finally, physicians should consider checking blood levels of hepatic transaminases, muscle enzymes (CK), and serum creatinine at least once for individuals on RYR therapy.

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## Disclosures

JHO-Chief Medical Officer, founder and major ownership interest of CardioTabs, a nutraceutical company that sells red yeast rice. MM

*Pain Management Mini-Series Part III*

# Procedural Sedation for the Non-anesthesia Provider

*by Quinn L. Johnson, MD & Robert Borsheski, DO*

**Establishment and ongoing oversight of a sedation policy should allow patients to receive safe and comfortable patient centered health care.**





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## Abstract

**Diagnostic and therapeutic procedures performed outside of the operating room can necessitate the administration of sedation by non-anesthesia trained personnel. Risks associated with procedural sedation can be decreased through proper patient evaluation and selection. Understanding sedative pharmacology, dosing and delivery, monitoring and airway rescue techniques are essential to safely provide sedation. Supervision of sedation policies should occur via a carefully constructed sedation policy and ongoing sedation committee evaluation and review to ensure adequate patient care.**

## Introduction

The need for procedural sedation in hospital and outpatient clinic settings has increased in the recent past, and those needs are projected to increase even further in the future.[1] The goals of sedation include reduction in patient anxiety, a decrease in discomfort, and an increase in patient satisfaction.[2] Physicians in emergency medicine, radiology, cardiology, pediatrics and gastroenterology utilize procedural sedation and analgesia without the assistance of anesthesiologists or anesthetists. Although there is ongoing controversy regarding which physicians should be allowed to administer sedation, the purpose of this review article is to highlight critical information and processes that should be considered by hospitals and physicians in creating and implementing sedation policies. The Joint Commission (TJC) and the Centers for Medicare and Medicaid Services (CMS) require each hospital or health system to implement, enforce, and monitor a customized sedation policy.[3] A multitude of specialty societies including the American Academy of Pediatrics, the American College of Emergency Physicians and the American Society of Anesthesiologists (ASA) along with twenty-four others[3] have issued guidelines regarding procedural sedation. Unfortunately, significant differences exist amongst the guidelines promoted by these various organizations. Regardless of the guidelines used, the safety of the patient must be the primary focus in the development of any sedation policy. Once sedation policies are implemented it is imperative that the sedation committee provide continuous oversight, periodic review of processes and credentialing of providers.

## Definitions

For sedation to be administered

Robert Borsheski, DO, Director of Acute Pain Services, and Assistant Professor of Anesthesiology at the University of Missouri administers a nerve block.



safely, it is crucial that the provider have a thorough understanding of the spectrum of consciousness. The definitions provided by the American Society of Anesthesiologists (ASA) are often referenced and are summarized here:

- Minimal sedation describes the unsupervised treatment of insomnia, anxiety or pain. Some examples may include a single oral sedative or analgesic. Minimal sedation carries minimal risk and is beyond the scope of this review.
- During moderate sedation, patients respond purposefully to a verbal command either alone or with light tactile stimulation. No interventions are required to maintain a patent airway and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
- Deep sedation is reached when patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired and patients may require airway assistance.
- When patients are not arousable even with painful stimulation, they are under general anesthesia. The ability to independently maintain ventilatory function is often impaired and they will likely require airway intervention. Cardiovascular function may also be impaired.[4]

Not only is it important to recognize the current depth of sedation, but the practitioner must have training and the ability to rescue the patient should a deeper level of sedation occur. Deep sedation should only be attempted by those qualified to rescue the patient in a state of general anesthesia.

## Pre-Sedation Patient Evaluation

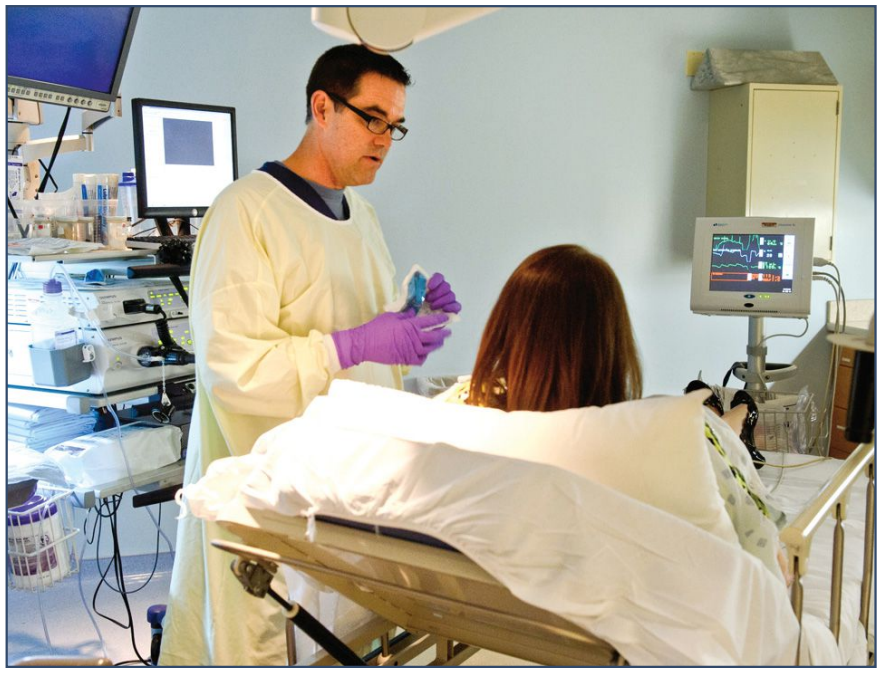
The risks most commonly associated with sedation include respiratory depression, hypoventilation, airway obstruction, aspiration and cardiovascular compromise.[2] While all patients are exposed to some risk, pre-sedation history and physical examination will help identify those patients who are at increased risk. In addition to performing a history and physical, other information should be verified including NPO time, obtaining a history of previous anesthetics, establishing IV access, and obtaining informed consent.[5] Every patient should also have a thorough airway examination.

Obesity is particularly problematic, has become increasingly common, and deserves special attention. Airway management in the obese patient can be difficult or even impossible. Obese patients have reduced functional residual capacities, making atelectasis and hypoxia common. The possibility of Obstructive Sleep Apnea (OSA) should be considered; any patient with OSA should be approached with a great deal of caution. Patients with OSA are particularly vulnerable to sedative medications and have a low threshold for airway collapse.[6] Even with minimal sedation, ventilation for these patients may become inadequate, leading to hypoventilation, hypoxia, and acidosis.[6] Potentially disastrous complications can be minimized with careful selection of medications, appropriate dosage, elevating the head of the patient's bed and diligent monitoring.[7]

A history of cardiovascular disease is relevant,

as many of the medications used in sedation have known cardiovascular depressant effects. There are also sequelae for inadequate sedation. For example, a patient with coronary disease may not tolerate tachycardia associated with pain. Patients with COPD or other pulmonary pathology need to receive special consideration, particularly with regard to respiratory depression. Other high risk groups include extremes of age, anticipated difficult airway, severe hepatic or renal disease, pregnancy or concomitant drug or alcohol abuse. Any patient with multiple comorbidities may require additional consideration [8] and may warrant consultation with an anesthesiologist.

A nurse in the endoscopy suite prepares a patient for a GI procedure.



## Monitoring

The crux of patient safety during sedation is diligent monitoring. In addition to other parameters that may be indicated given the clinical setting, each patient should be monitored for

1) level of consciousness
2) pulmonary ventilation
3) oxygenation, and
4) hemodynamic function.

All monitoring equipment should have functioning alarms with properly set limits and audible tones. Monitoring should begin with the administration of sedation, not at the start of the procedure. It is imperative that trained clinical personnel other than the proceduralist be designated for continuous patient monitoring.

As previously stated, the patient's level of consciousness may transition quickly and unintentionally between the defined stages of sedation throughout the procedure. This transition will be affected by the dose, timing and route of medications given, as well as changing degrees of stimulation caused by the procedure. Checking the patient's response to verbal and tactile cues is a simple task and should be repeated often. The ability of a patient to verbally respond to commands can be used to assure adequate breathing.[5] It is important to note that patients whose only response is reflex withdrawal from painful stimuli are deeply sedated and are approaching a state of general anesthesia.

Although related physiologically, pulmonary ventilation and oxygenation are actually distinct processes and monitoring should be considered separately. Inadequate pulmonary ventilation ushers a number of clinical risks such as hypercapnia, respiratory acidosis, tachycardia and both systemic and pulmonary hypertension. In addition to observation and auscultation, capnography may provide another layer of safety, particularly for deep sedation. While monitoring, it is important to ensure not only the presence of ventilation, but also the adequacy of ventilation.

Early detection of hypoxemia through the use of pulse oximetry can reduce the risks of both cardiac arrest and death.[4] Oximetry is superior to observation alone in detecting hypoxia, and its use should be considered routine. However, observation should not be abandoned. Depending on the cardiopulmonary reserve of the patient, changes in pulse oximetry often occur minutes after oxygenation is impaired, especially when supplemental oxygen is used.[5] Capnography may also have a role in

decreasing hypoxic events, as concluded in one study.[9]

Sedatives and analgesics can also have important effects on hemodynamic function. Blood pressure and heart rate monitoring should be regularly performed, most commonly at five-minute intervals. Continuous electrocardiography may also reduce risk, particularly during deep sedation. Many sedatives and analgesics may cause hypotension and/or bradycardia either directly or by blunting the autonomic responses to hypovolemia and stress. Inadequate sedation may also cause dangerous hemodynamic changes, namely catecholamine-mediated effects such as hypertension, tachycardia and arrhythmia.

## Pharmacologic Agents for Sedation and Analgesia

The keys to comfortably bringing a patient through a painful or stimulating procedure are, first, an understanding of what the patient needs are at any given point, and second, how to most effectively treat that need. For instance, if a patient is not anxious but is experiencing pain, it would be unwise to select a pure sedative such as midazolam or propofol. These medications have no analgesic properties and adverse effects will likely precede any benefit. In addition, adequate time must be allowed for the dose to take effect before considering additional dosing. Additional doses should not be given until the clinical response is observed to be inadequate. A brief review of medications commonly used is provided below.

## Benzodiazepines

One of the most commonly used classes of medication for procedural sedation is benzodiazepines (BZD), which includes drugs such as midazolam, diazepam and lorazepam. In addition to the intravenous route, BZDs are also bioavailable via oral, intramuscular, intranasal and sublingual routes. BZDs enhance GABA-mediated chloride flux in the CNS leading to hyperpolarization (and therefore depression) of neurons.[10] Although in higher doses they can be used to treat seizures, cause muscle relaxation and eventually induce a state of general anesthesia, they are very useful in lower doses for sedation and have a favorable safety profile. The desirable clinical effects include anxiolysis, anterograde amnesia and increasing levels of sedation with increasing doses. These endpoints are often achieved prior to the onset of undesirable effects such as cardiorespiratory depression. It is important to note however, that BZDs act synergistically with opioids to produce respiratory depression.[11] Brief periods of apnea may occur if given in a bolus rather than titrated. Benzodiazepines do not have any analgesic properties and therefore should not be used as the sole agent for painful or stimulating procedures.

Midazolam is the most potent and has the shortest duration of action of any BZD, making it a logical choice for procedural sedation. Common dosages are 1- 4 mg IV for an adult and 0.5 mg/kg PO for a child. Sedation and respiratory depression may be more intense and prolonged in certain populations, particularly the elderly. In the elderly, the respiratory side effects may linger several hours after the final dose.[12] Another advantage to the use of BZD's is the ability to reverse unwanted side effects with the selective antagonist flumazenil. A single dose of flumazenil (8 to 15 $\mu$g/kg IV) is rapidly effective, but with a duration of action of only 20 minutes, resedation is possible.

## Opioids

For centuries, opioids have been the gold standard for treating acute pain. The effect is achieved by binding presynaptic opioid receptors, which prevents the release of neurotransmitters via membrane hyperpolarization, thereby preventing an action potential. Presynaptic opioid receptors are of different subtypes and are found in varying locations. This complex receptor network accounts for the varying clinical effects of opioids. In addition to analgesia and sedation, opioid agonists also produce unwanted effects in a dose-dependent manner including: euphoria, miosis, respiratory depression, bradycardia, hypothermia, urinary retention, dysphoria, diuresis, itching, nausea and constipation.[13] Importantly, opioids do not offer anxiolysis or amnesia. Like BZDs, the effects of opioids are readily reversed with administration of a specific opioid receptor antagonist, naloxone. Doses of 1 - 4 $\mu$g/kg IV quickly reverse respiratory depression. Unfortunately, analgesia is also promptly reversed and this should be considered if the procedure has not yet concluded. Like flumazenil, the duration of action of naloxone (30 to 45 minutes) may be outlived by residual opioid.

The clinical differences between opioids are a result of their differences in pharmacokinetics. Though there are several options available, fentanyl is the most often utilized for painful procedures. When compared to morphine, fentanyl has higher lipid solubility and therefore potency. It also has a faster onset time and a shorter duration of action. Although the onset is considered fast, it does require

some patience on the part of the clinician. The time to equilibrium between plasma and CNS concentrations is 6.4 min, representing its peak effect.[13] Fentanyl is typically administered in doses of 0.5 to 2 μg/kg IV. Repeated or large doses may significantly prolong the effects of fentanyl. This is due to the saturation of inactive tissue sites, limiting the rate of redistribution away from the CNS.

## Ketamine

When the phencyclidine derivative ketamine was introduced into clinical practice in 1965, it was hoped to perform as a "complete anesthetic" since analgesia is included in its clinical effects. Though complex, the major mechanism is via inhibition of the NMDA receptor. When used in subanesthetic doses (0.2 to 0.8 μg/kg IV), ketamine can produce profound analgesia with minimal depression of ventilation and hemodynamics. There is a predictable increase in salivation and lacrimation, effects that can be mitigated with an anticholinergic agent. Ketamine causes relaxation of bronchial smooth muscle, making it a good choice for asthmatic patients. Its use has been limited by unpleasant psychomimetic effects, which are typically seen upon emergence. They include vivid dreams, visual, tactile or auditory hallucinations and may manifest as fear or confusion. Pretreatment with a BZD may lessen these experiences.[13] Although these reactions can be dramatic, they are relatively rare with analgesic doses in patients who do not have preexisting psychiatric disorders such as anxiety, PTSD or psychosis. Ketamine should be considered when there is increased concern regarding the adverse effects of opioids such as respiratory depression and bradycardia, which are virtually absent with ketamine. With reliable sedation and analgesia and lower incidence of untoward psychomimetic effects in children, ketamine is an attractive choice in the pediatric population.[14]

## Propofol

Most commonly used to produce a state of general anesthesia, the use of propofol has expanded to include sedation for intubated patients in the intensive care unit as well as for procedural sedation. The mechanism of action is similar to that of BZDs, via potentiation of the $GABA_A$ receptor complex. Propofol is insoluble in water and is prepared as a lipid emulsion. Because the emulsion can support bacterial growth, sterile technique should be utilized.[15] The glycerol in the emulsion can cause significant pain on injection, which is often worse in smaller, more peripheral veins. In a dose-dependent fashion, propofol causes hypnosis, amnesia, respiratory depression and hypotension. It is devoid of analgesia.

The ability to readily titrate the depth of sedation makes propofol an attractive choice. When used properly, a patient can be taken to a deeper state for the most stimulating portion of the procedure, receive superior sedation, and can be expected to recover quickly and smoothly at the conclusion.[3] A loading dose of 0.25-0.5 mg/kg is typically given followed by a subhypnotic infusion rate of 25 - 75 mg/kg/min, which commonly results in a stable level of sedation with minimal cardiorespiratory depression.[15] Propofol will potentiate the effects of opioids, BZD's, and barbiturates, requiring a decrease in the dosage required for sedation.[5] The risk with propofol is a narrow therapeutic range, as sedation can quickly progress to general anesthesia.[16] Because of the risk of respiratory depression and apnea, propofol should only be administered by individuals who are trained in airway management.[10] There is currently no agent that can reverse the effects of propofol.

## Dexmedetomidine

One of the newest options available for sedation, dexmedetomidine is a highly selective $\alpha_2$-adrenergic agonist.[5] Activation of these receptors within the CNS causes analgesia, at the level of the spinal cord, and hypnosis via the locus ceruleus. The sedation that occurs is the closest to a physiologic sleep state of any of the available agents. An attractive feature of dexmedetomidine is the minimal effect on respiratory drive. As with other drugs, the effect on respiration is synergistic when used in combination. Stimulation of $\alpha_2$ receptors in the CNS results in decreased sympathetic outflow. Bolus injection may produce transient decreases in systemic blood pressure and reductions in heart rate, which can be profound.[13] These effects are due to unopposed vagal output and can be countered with anticholinergic drugs. When compared to propofol, the target level of sedation often takes longer to achieve. The loading dose of 0.5-1.0 μg/kg is typically given over 10 to 20 minutes followed by a continuous infusion of 0.2 -0.7 μg/kg/hr.[5] Like with propofol, recovery from dexmedetomidine is rapid.

## Discharge from Care

Unfortunately, many of the complications of sedation can still occur after the patient has been discharged from care. Though discharge criteria should be established by each care site in accordance with specific patient populations and procedures, the basic principle is to have

the patient return as closely as possible to pre-sedation status for most if not all monitored parameters. There are several scoring systems in use to quantify recovery, such as the Aldrete Score.[17] The most important of these is recovery of mental, respiratory and cardiovascular function. It is important that each patient is continuously monitored by qualified personnel until recovery has occurred and those capable of managing complications must remain immediately available.[4] If reversal agents were used, the possibility of re-sedation must be anticipated when the reversal wears off. Patients should be accompanied home by a responsible adult who can detect the presence of complications of either the procedure or sedation. Written instructions should be provided including a phone number to call in case of an emergency.

## Conclusions

The use of sedation by non-anesthesiologists for procedures outside of the operating room requires proper pre-sedation patient selection and evaluation. Preparations for sedation include predetermining the depth of sedation required, monitor selection, choice of medication and dosing, and a plan to rescue a patient from deeper levels of sedation than originally anticipated. Post-sedation processes should include continued monitoring of the patient over a sufficient period of time to ensure appropriate resolution of sedative effects. Health Systems should establish sedation policies with input from anesthesiologist and incorporating recommendations from national organizations such as the ASA. Oversight of implementation, privileges, and use of sedation should reside with a sedation committee and include periodic chart reviews to ensure adherence to policy is present. Practitioners who administer sedation should demonstrate adequate training and maintenance of those skills on a periodic basis. Establishment and ongoing oversight of a sedation policy should allow patients to receive safe and comfortable patient centered health care.


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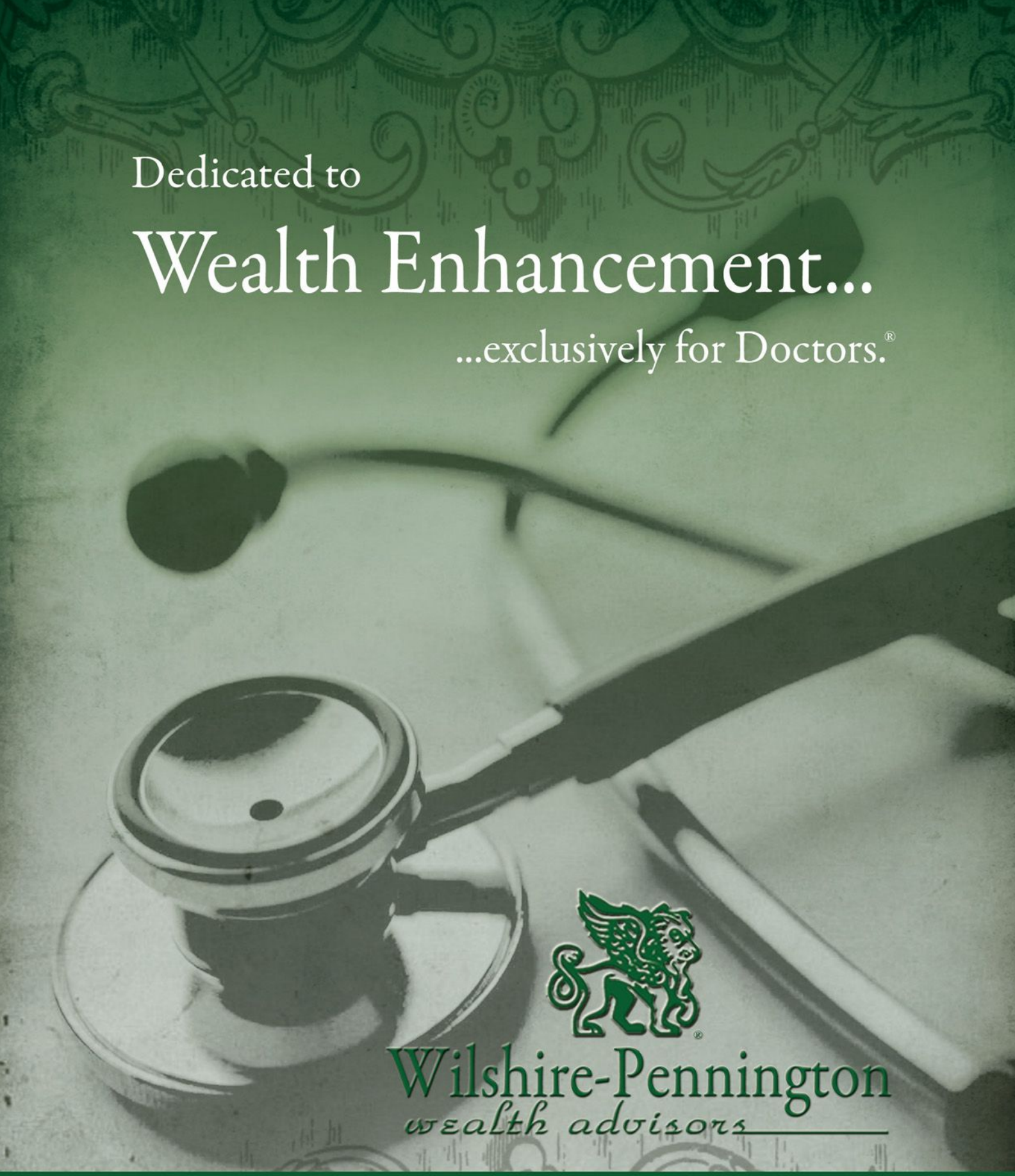

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## Disclosure

None reported.

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