Missouri Medicine
The Journal of the Missouri State Medical Association www.msma.org March/April 2014



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Hearts Breaking Over Marathon Running

Featured Scientific

Increased Coronary Artery Plaque Volume Among Male Marathon Runners
by Robert S. Schwartz, MD, Stacia Merkel Kraus, MPH, Jonathan G. Schwartz, MD, Kelly K. Wickstrom, BS, Gretchen Peichel, RN, Ross F. Garberich, MS, John R. Lesser, MD, Stephen N. Oesterle, MD, Thomas Knickelbine, MD, Kevin M. Harris, MD, Sue Duval, PhD, William O. Roberts, MD & **James H. O'Keefe, MD** 89

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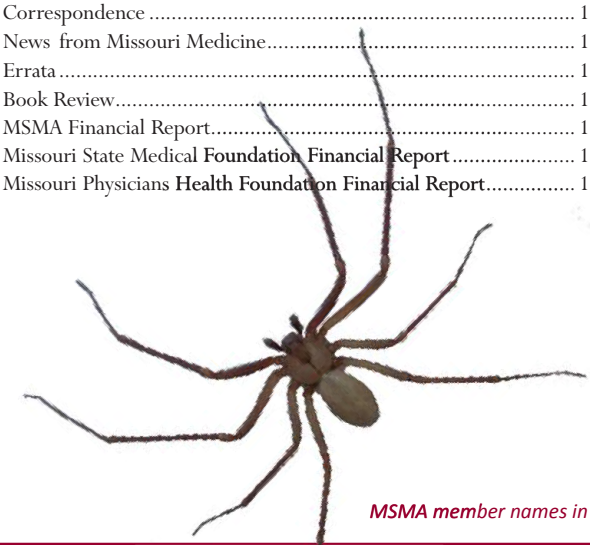
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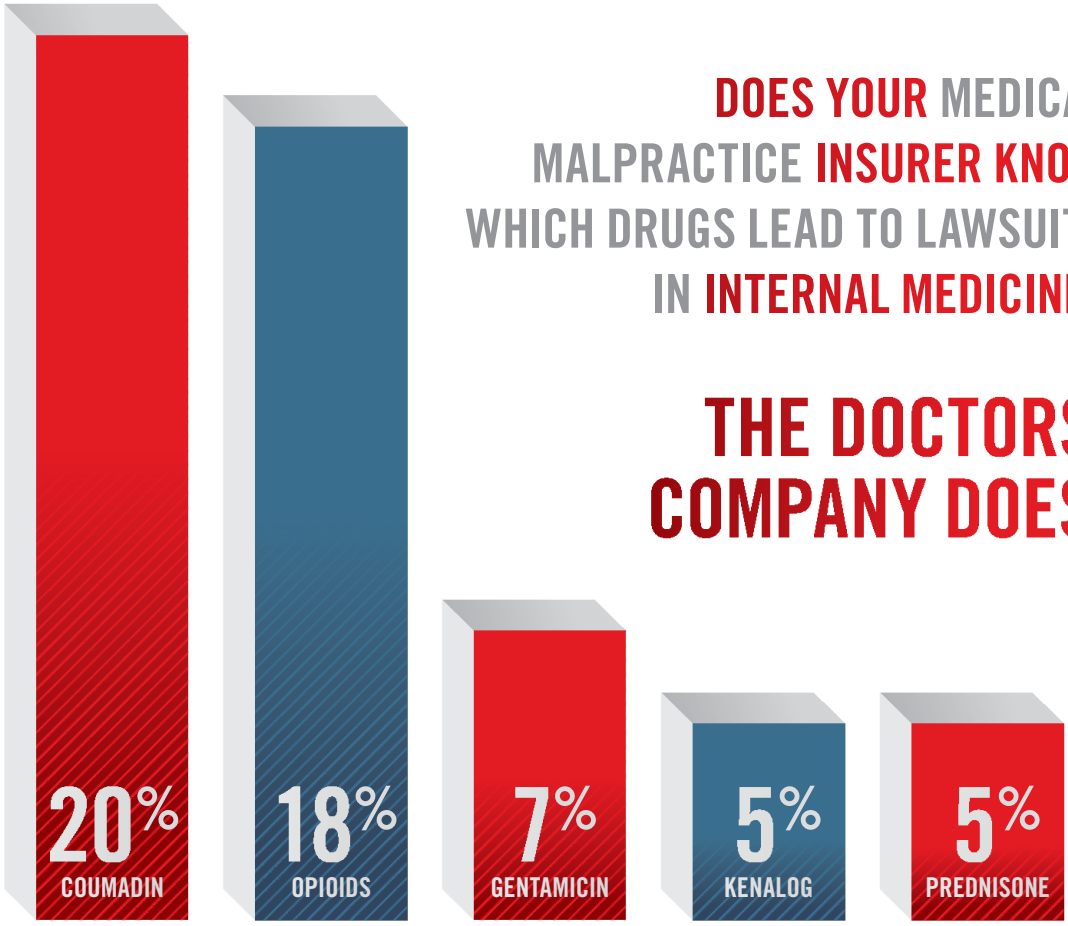
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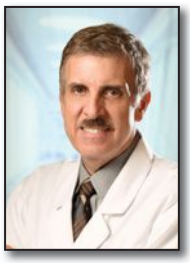
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Increased Coronary Artery Plaque Volume Among Male Marathon Runners

by Robert S. Schwartz, MD, Stacia Merkel Kraus, MPH, Jonathan G. Schwartz, MD, Kelly K. Wickstrom, BS, Gretchen Peichel, RN, Ross F. Garberich, MS, John R. Lesser, MD, Stephen N. Oesterle, MD, Thomas Knickelbine, MD, Kevin M. Harris, MD, Sue Duval, PhD, William O. Roberts, MD & James H. O'Keefe, MD

This study found that long-term participation in marathon training/racing is paradoxically associated with increased coronary plaque volume.





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Abstract

Background

Long-term marathon running improves many cardiovascular risk factors, and is presumed to protect against coronary artery plaque formation. This hypothesis, that long-term marathon running is protective against coronary atherosclerosis, was tested by quantitatively assessing coronary artery plaque using high resolution coronary computed tomographic angiography (CCTA) in veteran marathon runners compared to sedentary control subjects.

Methods

Men in the study completed at least one marathon yearly for 25 consecutive years. All study subjects underwent CCTA, 12-lead electrocardiogram, measurement of blood pressure, heart rate, and lipid panel. A sedentary matched group was derived from a contemporaneous CCTA database of asymptomatic healthy individuals. CCTAs were analyzed using validated plaque characterization software.

Results

Male marathon runners ($n = 50$) as compared with sedentary male controls ($n = 23$) had increased total plaque volume (200 vs. 126 mm3, $p < 0.01$), calcified plaque volume (84 vs. 44 mm3, $p < 0.0001$), and non-calcified plaque volume (116 vs. 82 mm3, $p = 0.04$). Lesion area and length, number of lesions per subject, and diameter stenosis did not reach statistical significance.

Conclusion

Long-term male marathon runners may have paradoxically increased coronary artery plaque volume.

Exercise might be best understood as a drug with powerful benefits, especially for cardio-vascular health. As with any potent drug, establishing the safe and effective dose range is critically important—an inadequately low dose may not confer full benefits, whereas an excessive dose may produce adverse effects that outweigh its benefits.

Introduction

Regular physical activity is a key component of a healthy lifestyle. Vigorous aerobic exercise is considered protective against coronary artery plaque development based on its favorable effects on many cardiovascular (CV) risk factors including lower resting blood pressure and heart rate, improved lipid profile and glucose metabolism, reduced body mass index (BMI), and association with healthier lifestyles such as eating a nutritious diet and avoiding tobacco.[1-3] Daily physical activity and high levels of cardiorespiratory fitness are also associated with lower inflammatory markers and better life-expectancy.[4-8]

Four decades ago, Thomas Bassler, MD, an American physician, notably hypothesized that marathon running confers immunity against coronary atherosclerosis.[9] Exercise might be best understood as a drug with powerful benefits, especially for CV health. As with any potent drug, establishing the safe and effective dose range is critically important—an inadequately low dose may not confer full benefits, whereas an excessive dose may produce adverse effects that outweigh its benefits.

Two recently published long-term large observational studies independently showed that runners, as compared to non-runners, have increased life expectancy. However, these longevity benefits were most significant for those obtaining moderate doses of running; individuals chronically performing high-intensity long-distance running appeared to lose the mortality benefit.[10, 11] Indeed, an emerging body of scientific data suggests that chronic, excessive, high-intensity exercise may induce oxidative stress and myocardial fibrosis, accelerate atherosclerosis, increase vascular wall thickness, and increase cardiac chamber stiffness.[12, 13] Demand ischemia related to significant coronary narrowing may also occur in endurance running, and rarely this may even result in myocardial infarction and cardiac arrest.[14, 15] Male marathon runners have also been shown to have paradoxically increased coronary artery calcified plaque as measured by computed tomography (CT) coronary calcium scoring.[16] However, a study using high resolution coronary computed tomographic angiography (CCTA) for quantifying coronary artery plaque volume in marathoners has not been previously performed.

Recent advances in CCTA provide quantitative, noninvasive assessment of coronary artery plaque, and permit accurate measurement of plaque volume and location. In this study we used CCTA to examine whether long-term marathon running in men is associated with quantitative coronary artery plaque differences compared to a sedentary control group.

Methods

The study was approved by the Institutional Review Board of Abbott Northwestern Hospital (Minneapolis, MN). It was a single-center observational study of male long-term, very long-distance runners who participated in the Twin Cities' Marathon (Minneapolis-St. Paul, MN). Eligible individuals were identified and invited to participate by reviewing marathon race records. After reviewing eligible subjects, participation thresholds were chosen as a minimum of 25 consecutive races for men.

A sedentary group of men was obtained from a coronary screening study of individuals who underwent CCTA scanning for clinical indications.[17, 18] All subjects in this group were self-reported to lead sedentary lifestyles. Attempts were made to match the marathon runners to the sedentary controls for coronary disease risk factors.

Inclusion Criteria

All subjects signed informed consent. Exclusion criteria were those who declined to participate, were allergic to x-ray contrast, and had serum creatinine ≥ 2.0. Scans were not scheduled if a subject had run a marathon within the previous two weeks or intended to run a marathon within the following two weeks (to avoid potential nephrotoxic effects from intravenous contrast, since marathon running is associated with a transient creatinine rise).[19]

Procedures

CCTA was performed per standard clinical practice using Siemens Dual Source or FLASH CT in a minimum x-ray dose protocol. At or near the time of the CCTA, the following procedures were performed: 12-lead electrocardiogram, height, weight, blood pressure, resting heart rate, serum lipid panel, historical life-style and risk factor questionnaire, and serum creatinine.

Data Analysis

CCTA scans were evaluated for all measurable plaque, both calcified and non-calcified. Plaque was manually identified and characterized for volume and stenosis severity using validated, commercial software on a commercial CCTA 3-D workstation (Vitrea, Vital Images, Minnetonka, MN).

Descriptive statistics were calculated and included means and standard deviations or numerical counts and percentages. Chi-squared or Fisher's exact tests were used to assess the statistical significance of categorical variables and t-tests or Wilcoxon tests were used for continuous variables where appropriate. The Shapiro-Wilk test was used to test for normality of continuous data. If normality assumptions failed, conclusions were based on non-parametric comparisons. A p value of ≤ 0.050 was considered statistically significant and all reported p values were two-sided. Statistical calculations were done with SAS software version 9.2 (SAS Institute Inc., Cary, NC).

Table 1
Demographic Characteristics of Subjects

Men			
Characteristic	Sedentary (n=23)	Marathon (n=50)	p value
Age, years	55.43 ± 10.39	59.44 ± 6.66	NS, 0.051
Systolic BP, mmHg*	134.00 ± 18.35	127.02 ± 13.74	NS
Diastolic BP, mmHg	79.30 ± 10.39	79.04 ± 9.40	NS
Heart Rate, bpm	70.83 ± 10.57	52.36 ± 9.31	< 0.001
Height, inches*	70.39 ± 2.10	70.10 ± 2.44	NS
Weight, kg*	96.8 ± 17.0	76.9 ± 11.5	< 0.001
BMI, kg/m^2*	30.29 ± 5.16	24.16 ± 2.88	< 0.001
Hypertension	15/23 (65.2)	12 / 47 (25.5)	0.001
Hyperlipidemia	19/23 (82.6)	22 / 47 (46.8)	0.004
Diabetes	4 / 23 (17.39)	0 / 50 (0)	0.008
History of Smoking, %	9 / 23 (39.1)	26 / 50 (52.0)	NS
Creatinine, mg/dl*	1.03 ± 0.20	1.15 ± 1.00	NS
Total Cholesterol, mg/dl*	183.56 ± 48.59	186.44 ± 28.83	NS
HDL, mg/dl	46.67 ± 8.86	58.02 ± 11.58	< 0.001
LDL, mg/dl*	108.13 ± 45.23	111.90 ± 26.09	NS
Triglycerides, mg/dl*	130.80 ± 63.00	83.36 ± 38.58	NS

Values presented are mean ± SD or n (%), p values from Fisher's Exact Test/T-test/Wilcoxon test for non-normal data
**Indicates failure of the normality assumptions based on Shapiro-Wilk test*
†BMI-body mass index, ‡HDL-high-density lipoprotein, §LDL-low-density lipoprotein, ||CAD-coronary artery disease

Results

Fifty male marathon runners and 23 sedentary male control subjects were enrolled. All male runners reported no CV symptoms and had no CV or coronary history. The marathoners and controls were similar in age, resting blood pressure, height, smoking history, serum creatinine, total cholesterol, and low density lipoprotein (LDL) cholesterol (p = NS for all) (See Table 1). Marathoners had significantly lower resting heart rate, weight, BMI and triglyceride levels, but had higher high density lipoprotein (HDL) levels, and were less likely to have a history of diabetes and hypertension (See Table 1).

Tables 2 and 3 summarize coronary CT lesion analysis. There were 46 lesions in 12 of the 23 sedentary subjects and 95 lesions in 30 of the 50 marathon participants. There was no difference in lesion prevalence between groups. Male marathon runners however had paradoxically increased total plaque volume (200 vs. 126 mm^3, $p = 0.002$), calcified plaque volume (84 vs. 44 mm^3, $p < 0.0001$), and non-calcified plaque volume (116 vs. 82 mm^3, $p = 0.04$) (See Figure 1). Lesion area,

Table 2
Lesion Prevalence across Runners and Sedentary Subjects

Lesion Prevalence - Men			
Characteristic	Sedentary (n=23)	Marathon (n=50)	p value
Number of lesions	47	95	-
Lesion prevalence	12 (52.2)	30 (60.0)	NS

Values presented are mean ± SD or n (%)
p values from Fisher's Exact Test/T-test

Table 3
CT derived Lesion Characteristics

Lesion Data - Men			
Characteristic	Sedentary (n=47 lesions)	Marathon (n=95 lesions)	p value
Lesion area*	43.4 ± 26.0 (44)	46.9 ± 24.2 (94)	NS
Lesion diameter*	42.0 ± 22.4 (43)	41.7 ± 19.9 (94)	NS
Lesion length*	15.1 ± 8.0 (43)	20.0 ± 17.3 (94)	NS
Plaque volume*	125.5 ± 80.5 (46)	200 ± 144.2 (95)	0.002
Calcified Plaque volume* mm^3	44.0 ± 36.8 (46)	83.8 ± 67.7 (95)	< 0.0001
Non-calcified Plaque volume mm^{3*}	81.5 ± 58.1 (46)	116.1 ± 95.7 (95)	0.039

p values from T-test/Wilcoxon test for non-normal data
**Indicates failure of the normality assumptions based on Shapiro-Wilk test*

diameter stenosis, and length differences did not reach statistical significance between the two groups.

Discussion

The association of decades-long marathon training/racing with coronary artery plaque was examined in this study. Few prior studies have focused on this association, and none using plaque quantitation by CCTA. We found that long-term marathon running in men may not engender protection against coronary artery plaque development, despite conferring advantages in many traditional coronary risk factors including favorable changes in lipid levels, glucose metabolism, and blood pressure. To the contrary, this study found that long-term participation in marathon training/racing is paradoxically associated with increased coronary plaque volume (despite comparable plaque prevalence).

A recent study found the incidence of sudden death in marathon running is approximately 1 in 100,000 participants,[15] with coronary artery disease (CAD) accounting for the majority of fatalities.[14] Fortunately, these deaths, though tragic and disturbing, are rare. However, the bigger concern may be the fact that excessive exercise ultimately deprives the individual from reaping the significant longevity benefits conferred by moderate exercise.

The Copenhagen City Heart Study followed 1,878 runners and 10,158 non-runners for up to 35 years.[10] The runners had an impressive 44% lower risk of mortality during follow-up, with an increase in life expectancy of about six years for both genders. Importantly though, U-shaped curves were apparent for mortality with respect to dose of running, whereby the benefits of running were most significant for those who jogged between 1 to 2.5 hours per week, at a slow to moderate pace, with a frequency of about three times per week.[10] In those runners who were performing higher volume, higher intensity running, the long-term mortality rates were not significantly different from non-runners. In other words, excessive running may have abolished the remarkable improvements in longevity conferred by lower doses of running.

Strikingly concordant data were seen in a large decades-long observational study of 54,000 Americans.[11] Highly significant mortality reductions were seen in the runners compared to the non-runners, but U-shaped curves again showed that the lowest mortality rates were seen in those running 5 to 20 miles/week, and that the longevity benefits of running completely disappeared with distances greater than 25 to 30 miles/week.

Still, the mortality rates in the high mileage runners were similar to but did not exceed those for sedentary individuals).[11]

Cardiac over-use injury is a term that we have proposed for problems that arise with chronic excessive high intensity exercise. Reports have documented myocardial fibrosis and scarring, potentially dangerous rhythms, and accelerated coronary atherosclerosis (a constellation of pathology which has been labeled Pheidippides' Cardiomyopathy by Peter McCullough, MD).[12, 13, 19] The number of individuals running in marathons and other extreme endurance events has been rising dramatically during the past 40 years (See Figure 2).[12, 13] We suspect some runners might choose shorter, less exhausting challenges if they were aware of the potential adverse cardiac effects of chronic extreme endurance efforts.

The metabolic and mechanical stresses produced by excessive running could constitute a causal role in accelerated atherosclerosis. Runners who train and race over very long-distances experience protracted elevations in heart rate, blood pressure, cardiac output, and atrial and ventricular volumes for up to several hours per day. Intense exercise generates large quantities of free-radicals that outstrip the buffering capacity of the system after approximately one hour of vigorous continuous exercise, leaving these individuals susceptible to oxidative stress, atherogenic modification of cholesterol particles, and endothelial dysfunction.[20] Ultra-endurance efforts also cause multiple other disturbances within the system including sustained elevations of catecholamines and resultant coronary vasoconstriction, protracted sinus tachycardia which reduces the diastolic filling time of the coronary arteries, changes in free fatty acid metabolism, lactic acidosis, and other metabolic derangements.[12, 13, 19]

Figure 1
Marathoners had significantly more total coronary plaque volume, non-calcified plaque volume and calcified plaque volume compared to control subjects.

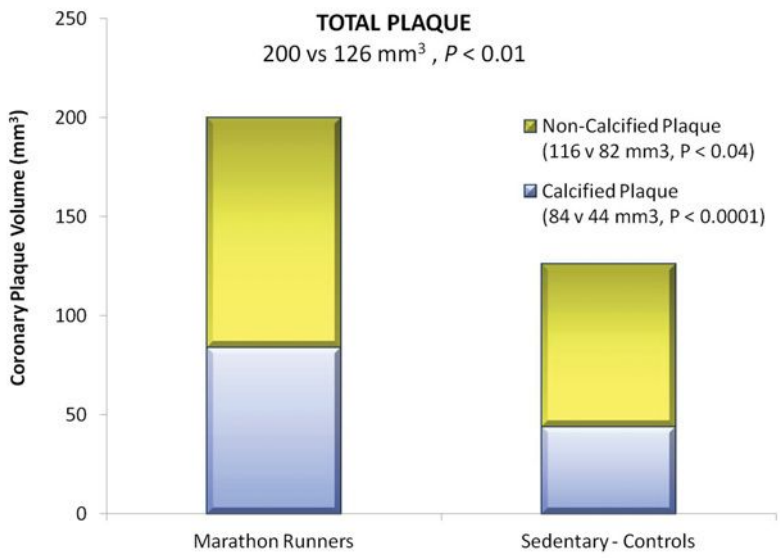
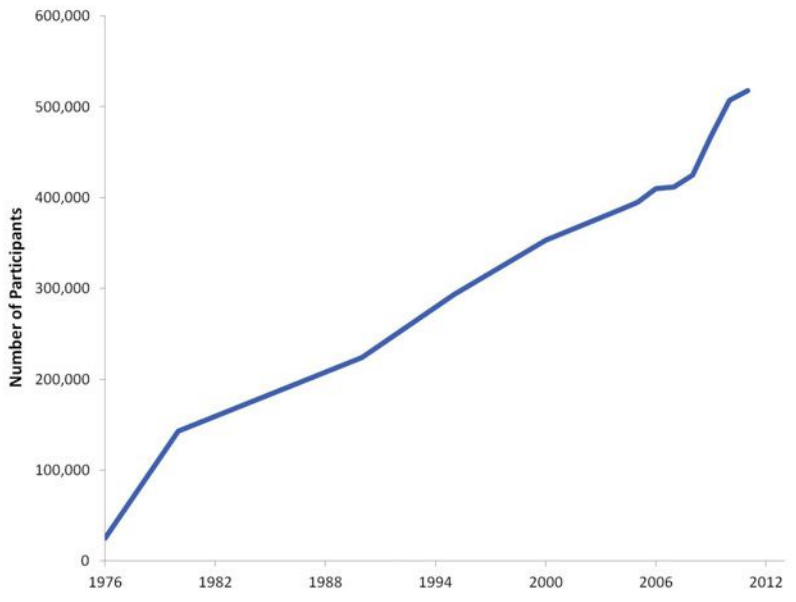


Figure 2
Marathon running trends in the United States from 1976 through 2011.



Limitations

The control group, although matched for age, gender and several CV risk factors, was unable to be

matched to the marathoners for resting heart rate, weight and HDL levels, likely the result of chronic high intensity aerobic exercise. Still, these differences would be expected to protect against atherosclerosis, thereby favoring the marathoners. However, the sedentary controls had significantly less coronary plaque despite the marathoners' more favorable CV risk factors.

This was a single-center observational study, based on recruitment from known runners who chose to participate. However, a study that randomly assigned individuals to either run marathons for 25 years or be sedentary for 25 years is practically impossible, and will never be done. Thus, a cause-and-effect relationship between marathon running and accelerated coronary plaque development cannot be established. Nonetheless, multicenter studies comparing coronary plaque volume in larger numbers of marathoners and matched sedentary control subjects would be of great interest.

Conclusion

Long-term training for and competing in marathons may in men be paradoxically associated with accelerated coronary artery plaque formation.

Acknowledgments

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Disclosures

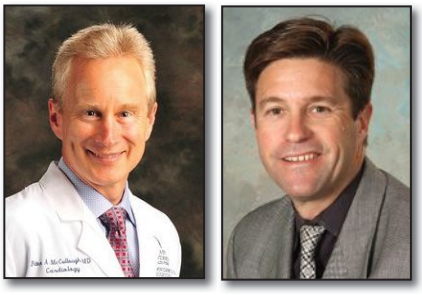
None reported.

MM

Coronary Artery Plaque and Cardiotoxicity as a Result of Extreme Endurance Exercise

by Peter A. McCullough, MD, MPH & Carl J. Lavie, MD

To summate present knowledge in early 2014, studies support a potential increased risk of coronary artery disease, myocardial fibrosis, and sudden cardiac death in those with considerable experience as marathoners (25 or more races completed).



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Fallible Logic: *'Some Exercise is Good, More Must Be Better'*

Aerobic exercise and fitness has been generally viewed in a positive light among the lay public and health care providers for decades.[1] The impressive and consistent reductions in cardiovascular (CV) mortality among those fit compared to sedentary individuals has lead to many conclusions which now appear to be challenged with recent studies.[2] The previous chain of logic was that if CV morbidity and mortality is reduced among those with higher physical activity (PA) and exercise training (ET) and who are more fit (See Table 1),[3] then there must be a reduction in atherosclerosis in terms of presence or absence or potentially a reduction in the general plaque burden. Furthermore, if some exercise is good, then more should be better. Thus, marathoners, among all recreational athletes, should be most free of atherosclerosis. The report by Schwartz and colleagues[4] in this issue of *Missouri Medicine* is a sobering reminder that all forms of deduction or chains of logic in clinical medicine should be challenged with scientific investigation.

Among those with considerable experience as marathoners (25 or more races completed), the cases in this study undoubtedly had many years of endurance training and cumulatively logged distances traveled that could be 100-fold greater than average sedentary individuals. Thus, the summative physiological environment of the marathoners was no doubt extremely different than the control group of sedentary individuals. As the authors pointed out, exercise is a transient oxidative stress on the systemic vasculature, creates greater shear stress in the coronary arteries, and is associated with a variety of additional adverse effects which are short-term, provided the aerobic activity is brief.[4] The important point is that marathoners have sustained increases in aerobic activity and cardiac demand for hours at a time. Therefore, the biologic plausibility for these factors to promote atherosclerosis is tenable, despite improved risk factor profiles, and this thread of concern has been evident in the literature for several decades.[5] It is important that CV risk factors were developed as associated variables for binary events of nonfatal myocardial infarction (MI) or CV death, not for the presence or absence of atherosclerosis.[6] Thus, despite the healthier CV risk profiles on the surface, the burden of atherosclerosis and potentially worrisome noncalcified plaques which could be more susceptible to rupture and result in MI is a reality that must be understood among adult marathoners and their physicians.[7]

Table 1
Potential Benefits of Physical Activity and Exercise Training

Improvements in Exercise Capacity
- Maximal Oxygen Consumption (Peak VO2)
- Estimated METs

Improvements in Lipids
- Total cholesterol
- HDL-C
- LDL-C
- Triglycerides
- Total cholesterol/HDL-C
- LDL-C/HDL-C

Reduction in Obesity Indices
- Weight
- Percentage Body fat
- Body Mass index

Improvements in Blood Rheology
- Reduction in Homocysteine Levels
- Improvement in Viscosity

Improvement in Psychosocial Factors
- Depression Score
- Anxiety Score
- Hostility Score

Major Morbidity and Mortality
- Reduction in Overall Mortality
- Reduction in Hospital Costs
- Reduction in Non-Fatal Myocardial Infarction

Sudden Cardiac Death

Besides potential detrimental changes in the coronary arteries, there are several other forms of cardiotoxicity associated with marathon running or extreme endurance exercise (EEE).[2, 8-10] Perhaps the most serious is sudden cardiac death (SCD). Although episodes of SCD often generate considerable publicity in major running road races or other long distance endurance events, SCD remains relatively uncommon.

A recent study reviewed all marathons and half-marathons in the United States from 2000 - 2010 (10.9 million runners; 59 cardiac arrests) and reported that SCD occurred in only 0.54/100,000 participants.[11] Although other studies suggest that the true occurrence may be two-to four-fold higher than this,[12,13] due to the fact that the Kim et al.[11] data may be contaminated by large numbers of half marathoners and only accounts for SCD during the race itself and not soon afterwards, still the fatality in marathons is relatively uncommon, but still "too high." The fatality rate of triathlons is approximately two-fold higher than that of marathons, but largely because of increased CV events and SCD during the swim portion of the race.[14] The high catecholamine state of competition superimposed on forms of either preexisting training-induced structural myocardial abnormalities is the most tractable explanation for cases of SCD after common causes such as hypertrophic cardiomyopathy, coronary artery disease, anomalous coronary arteries, channelopathies, and other etiologies are excluded.

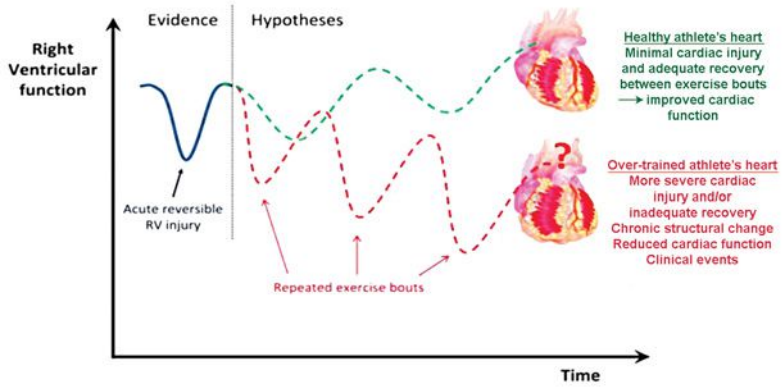
Adverse Effects of Cardiac Structure and Function

Besides potential adverse effects on CAD discussed above, EEE has potential adverse effects on cardiac structure and function (See Figures 1 and 2).[2,8-10] In fact, animal studies have suggested considerable potential cardiotoxicity of EEE.[15,16] In one recent study, rats were trained to run strenuously for 60 consecutive minutes daily for 16 weeks.[16] Compared with control rats, the exercise rats developed left ventricular (LV) hypertrophy, right ventricular (RV) hypertrophy, diastolic dysfunction, and dilation of both atria, as well as collagen deposition in the cardiac chambers. Ventricular tachyarrhythmias were inducible in 42% of the running rats compared with only 6% of the controls ($p=0.05$). After de-training, the adverse changes and elevated electrical irritability largely reversed.[16]

Similarly, adverse structural remodeling following EEE has been noted in humans.[2,8-10] For example, following a marathon, studies have demonstrated that almost 30% of runners develop acute dilation of cardiac structures, especially the RV and right atrium, and dysfunction of both the LV (at least in the ventricular septum) and, especially, the RV.[2,8-10,17,18] Serologic markers of cardiac damage, including cardiac troponin and creatinine kinase myocardial band, two enzymes released in acute MI and used to diagnose MI, and B-type natriuretic peptide (or BNP), which is used to monitor patients for heart failure, are elevated in close to 30% and up to 50% of participants during a marathon.[2,8-10,17,19-22] Although these abnormalities typically reverse within days of an acute bout of EEE, concern has been expressed that repeated episodes may lead to myocardial cell damage at sites of myocyte slippage of one cell above another due to loss of integrity of desmosome connections, and chronic multiple injuries may lead to stimulation of resident fibroblasts to produce extracellular collagen resulting in patches of fibrosis, the substrate for anisotropy and lethal arrhythmias. The predisposing genetic substrate, dose, and duration of endurance training and competition are all unknown, but

based on the totality of evidence, we believe that high levels of EEE may predispose some individuals to long-term cardiotoxicity resulting in more extensive coronary atherosclerosis and calcification as well as myocardial fibrosis.[23]

Figure 1
Potential impact of repeated bouts of ultra-endurance exercise on right ventricular structure and function. Reproduced from Patil et al. [10]

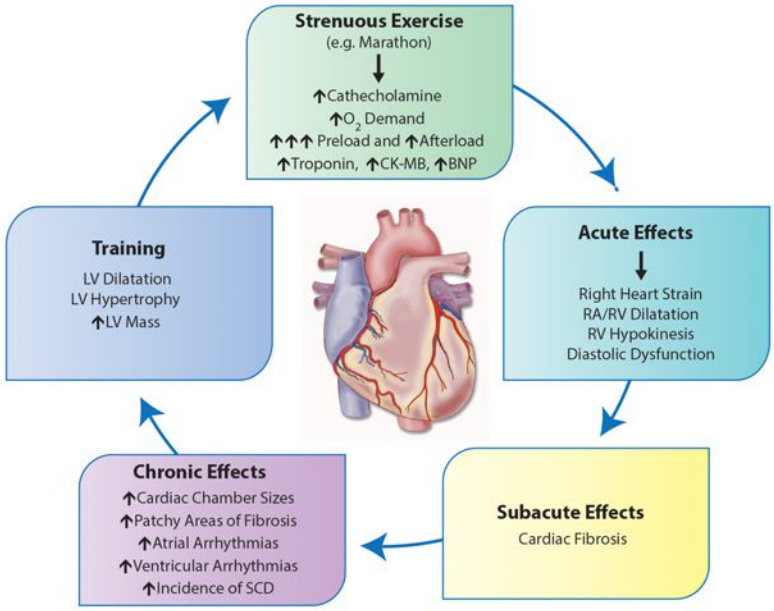


Original figure from Sharma S, Zaidi A. Exercise-induced arrhythmogenic right ventricular cardiomyopathy: Fact or fallacy? European heart journal. 2012;33:938-940

Proarrhythmic Environment of Training and Competition

It appears that in some athletes, the adverse cardiac remodeling induced by EEE can create an arrhythmogenic substrate, some of which may increase the risk of dangerous ventricular arrhythmias and SCD.[2, 8-10,18,24] At times, malignant ventricular arrhythmias can develop in competitive athletes, similar to that present in patients with familial arrhythmogenic RV dysplasia, possibly due to sustained volume overload of the right sided cardiac chambers for several hours.[25] This in combination with high levels of catecholamines may alter the arrhythmogenic potential in some patients. In addition, it has been reported that heavy endurance exercise, including EEE, increases the rate of atrial fibrillation by as much as five-fold, presumably due to similar mechanisms of periodic and sustained volume overloading of the left atrium resulting in fibrosis and electromechanical remodeling.[2, 26-29]

Figure 2
Proposed pathogenesis of endurance athlete's cardiomyopathy. RA=Right atrium, RV= Right ventricle, LV= Left ventricle, SCD= Sudden Cardiac Death. Reproduced from Patil et al. [10]



Current Recommendations

Clearly, the United States and most of the Westernized World are currently plagued by lack of physical activity and exercise training.[23] Certainly, lack of physical activity and exercise training are much greater problems for our society than is the potential adverse effects of excessive endurance exercise. We must recognize that most participants in excessive endurance exercise, including marathon runners, are not doing this activity for health reasons alone, but are driven by the thrill of competition, fellowship, and the attainment of personal goals. In a similar vein, people jump from planes and mountains, race cars and boats, and participate in many other sports or recreational activities, without the primary purpose being health improvement. We should stress that the benefits of PA and ET seem to occur and be maximized after the first 40-60 minutes,[2, 8-10,23] and more prolonged ET, such as EEE in marathon runners and triathletes, improves athletic performance and burns calories, but does not typically promote additional health benefits and as we have pointed out, may cause harm including greater risk of CAD as

reported by Schwartz and colleagues,[4] and cardiac fibrosis and SCD as published by others.[2, 8-10] Simply stated, the platform of "more is better" for aerobic exercise training recommendations is not supportable at this time.

Future research will need to take this work a step further to really understand the relative stability or instability of atherosclerosis among various patient populations. It is possible that the original chain of logic is still somewhat intact; that is, marathoners may have relative freedom from myocardial infarct, not because they are free of atherosclerosis, but because atherosclerosis that forms in those who exercise regularly is in some way "protected" against instability and MI. In addition to better phenotypic characterization, the future holds the promise for genetic susceptibility testing to understand individual profiles that are very favorable towards endurance training and those that potentially indicate harm to both the coronaries and the myocardium with this form of exercise and competition.[30] To summate present knowledge in early 2014, studies support a potential increased risk of coronary artery disease, myocardial fibrosis, and sudden cardiac death in marathoners.[2,5, 8-10,31-33]

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Disclosures

None reported. **MM**

Pheidippides' Final Words: "My Feet Are Killing Me!"

by John C. Hagan, III, MD

In the long run, you may end up with a broken heart.



Missouri Medicine Editor John C. Hagan, III, MD, was very confident that his long-distance running would guarantee a healthy heart. He now believes 45 years of maximum endurance exercising contributed to his atrial fibrillation and high coronary artery calcium score. Above, Dr. Hagan runs the Kansas City Hospital Hill Half Marathon in 1988.
This is a modification of an editorial that appeared in *Missouri Medicine: The Journal of the Missouri State Medical Association* in July/August 2012.
Contact: jhagan@bizkc.rr.com

Let me "run" something by you. Whoa, I forgot, that was the old Marathoner/100-mile Bicyclist/Half-Ironman Triathlon® -Me talking. Let the new Easy-Exercising-Me "walk" you through this.

A sea of change is occurring in the understanding of heart disease and extreme endurance exercise like marathon running. A growing number of influential cardiologists, including *Missouri Medicine's* Preventive Medicine Editorial Board member James H. O'Keefe, MD, and his collaborators, report persuasive evidence that prolonged (>one hour) maximal or near maximal aerobic exercise, especially after age 50, may be lead to heart damaging atheroma in the myocardium and coronary arteries. (See pages 85-92 for Schwartz et al. article and McCullough/Lavie editorial) Part of this body of evidence is the finding that veteran (a code word for "older") marathoners and other endurance athletes have higher than normal coronary artery calcium scores (CACS) and rates of atrial fibrillation. Been there; got that!

I have been a long-distance runner since about 1967. If I didn't run at least 12 miles at a time, I felt it was a wasted effort. I was especially influenced by Kenneth Cooper, MD, and his book "*Aerobics*" and the pioneering work of Scottish physician Jeremiah N. Morris, MD, who established the inverse relationship between mild to moderate physical activity with cardiovascular disease, and American preventive cardiologist Jeremiah Stamler, MD, who first coined the term "risk factors" for the association of hypertension, obesity, lack of exercise, and lipid abnormalities with heart disease.

Running Pied Pipers appeared. Among them was pathologist Thomas Bassler, MD, who, in 1977, stated that running long distances prevented coronary artery disease and that no marathoner had died of a myocardial infarct in a 10-year study he conducted. This was first disproven by Timothy Noakes, MD, who presented four marathoners who had died of autopsy-proven coronary artery disease. Popular running author Jim Fixx, at age 52 in 1984, died of a heart attack while running; Olympic marathoner and three-time winner of the New York Marathon Alberto Salazar, 47, was technically dead for 14 minutes due to a heart attack before being revived. He was found to have extensive coronary artery disease. (Note to self: pay attention to things like that next time).

Nevertheless, the number of distance runners has swelled and races are longer and longer: 10 Kilometer, half-marathons, marathons (26.2 miles), 100 milers (including the "Leadville Colorado 100" that is run at altitudes between 9,200 feet and 12,600 feet), and the world's current longest certified foot race, the Self-Transcendence 3,100 Miler. It requires that runners complete the distance within 51 days or an average of 60.68 miles/day.



Figure 1 - Dr. Hagan in the 1993 Midwest Triathlon Championship, 1.2-mile swim, 56-mile bike, 13-mile run. He finished in 7 hours 10 minutes placing third in his age group and 34th overall.

My first published paper (1974) in *Resident and Staff Physician* "Survival of the Fittest" was about using exercise to reduce the risk of heart disease. Subsequently, I bought into the 'running more miles means better cardio-vascular health' movement. Thinking I was giving my heart just what it needed to prevent disease, I ran more than 25 Hospital Hill Half Marathons, four marathons and two Half Ironman Triathlons (See Figure 1). For many years I weekly averaged about 30-40 miles of running.

Ken Cooper, MD, to his great credit, in 1985, was among the first to express concerns about running very long distances at an all-out effort. Cooper said that anyone running over 15 miles per week was pursuing something "other than fitness." He also expressed concerns that long distances at maximum effort might suppress the immune system and predispose to neoplastic disease. Several very prominent long-distance runners, such as New York City Marathon director Fred Lebow and Olympic Marathon Champion Greta Waitz died relatively young of cancer. Cooper also felt that most, if not all, of the benefits of aerobic exercise can be obtained from much shorter exercise periods and at less than "all out" intensity. Bingo! Please re-read that last sentence, it will be the new paradigm.

At age 61, my heart served notice of overuse and abuse when I developed atrial fibrillation as described in a previous *Missouri Medicine* editorial (Fascinating Rhythm: Atrial Fibrillation—The Beat Goes On. 2006;103: 200-201)

So-called "lone" atrial fibrillation is more common in endurance athletes such as marathoners, long-distance cyclists, and cross country skiers.

I have for decades subscribed to *Runner's World,* the publication for runners. In the last 10 years it seems there have been more stories of marathoners and longer distance racers having heart attacks and/or death while running. There have been articles and letters in *Runner's World* recommending that runners determine their Coronary Artery Calcium Score (CACS). Coronary artery calcium is a presumed proxy for atheroma and the higher the number (the Agatston Scale is used: a perfect score is zero; 100 or less is mild calcification) the greater the heart artery plaque burden is felt to be. In large random populations this translates into higher rates of cardiac events (cardiac death, clinical arrhythmias, angina or myocardial infarcts). A father/son team of running cardiologists from Minnesota found marathoners had higher CACS than age matched non-runners. Europeans researchers confirmed this finding. CACS can be determined by a quick, easy and inexpensive test called a Heart CT. It is an ongoing controversy among cardiologists and public health officials when this test should be obtained. It seems running up the score is unsportsmanlike conduct.

I had asked my former cardiologists about having a heart CT, and mentioned that a disturbingly number of marathoners were reporting personal high CACS. More than a few with high CACS had work ups revealing coronary artery disease so severe that angioplasties, stents, and even coronary artery by-pass grafts were needed. I was told the heart CT would not tell those cardiologists anything they didn't already know or change how I was treated. Being basically a compliant patient I demurred.

By pure serendipity my ophthalmology practice changed health insurance plans and I had to find another cardiology group. When I again broached the heart CT question, my new cardiologist told me I could have the test

done as a walk-in any day that was convenient for $50. I soon took the test with almost a smug expectation of zero coronary calcium. The results left me 'broken-hearted.' A nurse clinician gave me the disturbing news immediately after the test that my Agatston Score was 1606. OMG, the proverbial heart of stone. I have more calcium in my heart arteries than most people have in their long bones. The cardiologist was sufficiently alarmed that he called me at home and asked me to come to his office immediately.

Another intensive round of heart tests were normal. However, this time rigorous interventions were done: I went to lipid clinic and changed a good diet into a fabulous diet. I went from a somewhat over-weight 192 pounds (BMI = 25.3) to a svelte 177 (BMI 23.3). My cholesterol was good but triglycerides borderline high. I went on statins. My lipid profile is so good I now take low dose statins every other day. My blood pressure medications were tweaked to superb levels and, with the weight loss, gradually cut back also. For the record, I am a lifetime non-smoker.

My new heart-friendly exercise program (five to six days/week walking, swimming, bicycling, weight-lifting) is never done at maximum effort and, except for moderate speed walking (with two minute stand-still recovery breaks), is less than an hour's duration. I've updated my estate planning; I take time to smell the roses every day; I'm hoping, as Agastston himself suggests, that my coronary artery plaques have been stabilized with intact lumen and any soft, lipid-filled thrombosis-causing plaque eliminated. *Missouri Medicine's* published study by Schwartz and others seems to indicate for some veteran marathoners that is not the case.

So, what's the message here? Physicians, including me, have the medicine (exercise) correct, but we definitely have got the dosage - faster and further - wrong. This happens all the time. Let me give you an example from the marathon world. In the mid-1960s most marathon race day deaths were from heat stroke brought on by inadequate hydration. The sustained message to runners was to drink as much water as possible during the run. In recent marathons most deaths have been from drinking too much water leading to fatal dilutional hyponatremia. Exercise is the same: too little can kill you, too much can kill you. Regular, moderate exercise is as close to a magic elixir as we are likely to discover.

I understand statistics; I understand the tyranny of small numbers and under-powered studies; here N = 1 and one is the loneliest number. Thus qualified, I believe 45 years of long-distance running at near maximum effort failed to prevent coronary artery disease and likely is the cause of my history of atrial fibrillation and high CACS. Almost all of my many relatives live to their mid- to late-80s. My maternal grandmother made it to 94. Workers all, none exercised.

With the qualifications that I am an ophthalmologist by way of general practice and my heart story anecdotal evidence; I present my conclusions on 'preventive cardiology' delivered from an editorial bully pulpit.

For most people, 30 minutes of walking, even if broken into multiple shorter intervals, five to six days per week will accrue almost all the benefits of exercise with the lowest possible risk of adverse events. It's a regimen that might reasonably be sold to an increasingly slothful and obese public. Please view "23 and One Half Hours" on You Tube and recommend it to your patients. Go here for the link: www.youtube.com/watch?v=aUaInS6HIGo

Maximum effort, endurance exercises/sports greater than one hour duration should be discouraged, especially in those over 40. Patients should be informed of the potential that such activities can cause increased rates of cardio-vascular disease even death in some participants.

The heart CT should be used more often as a tool for finding unsuspected coronary artery disease. Most endurance athletes over 40 should have a heart CT and be considered participating in a higher cardiovascular event risk activity.

After 40 most people should be on a statin (every cardiologist I know is so why shouldn't our patients?) and a baby aspirin. Hypertension, even pre-hypertensive states, should be treated.

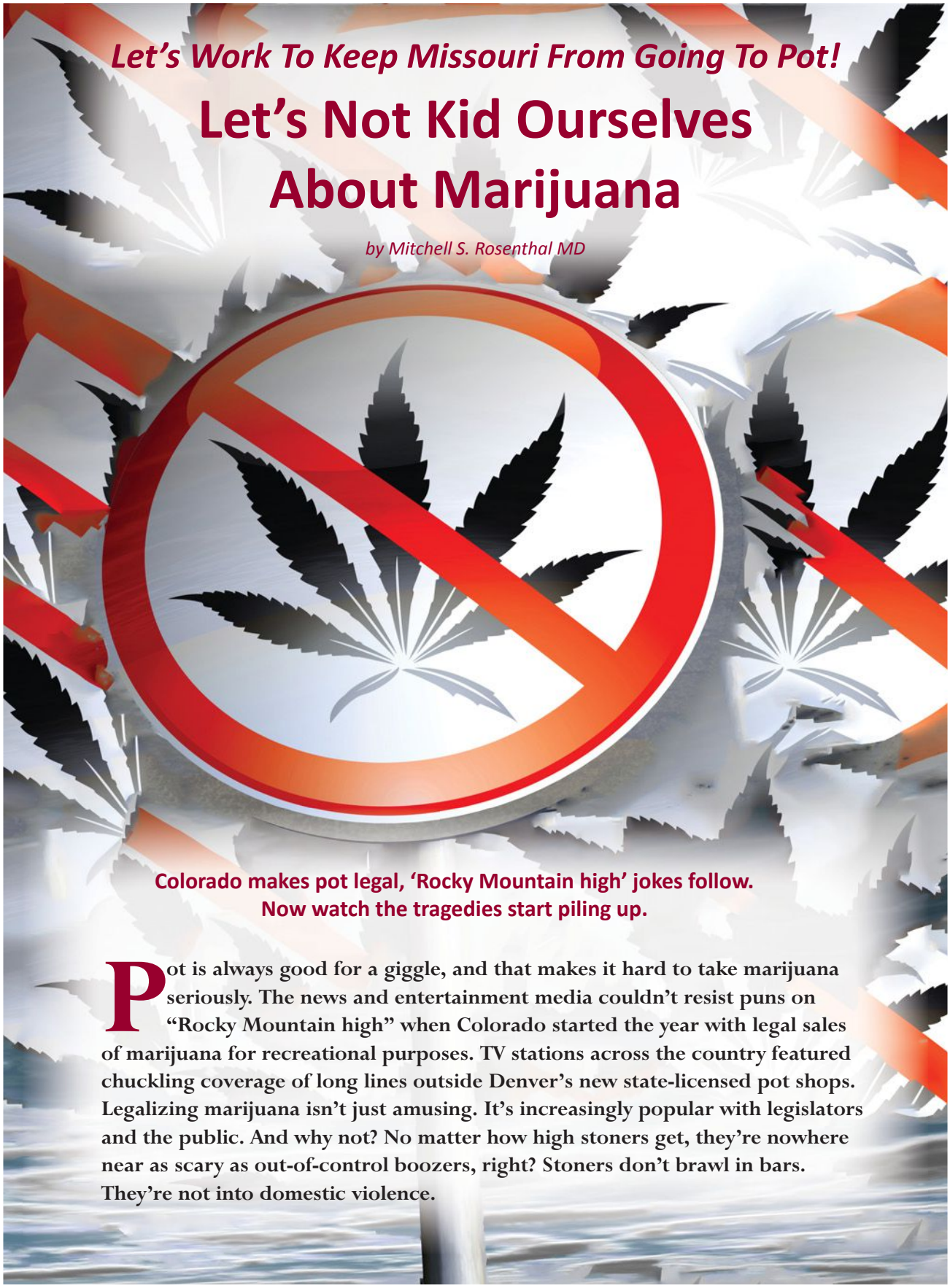
Despite the personal discomfort it often engenders, physicians must regularly address our patients' problems of obesity, poor diet, smoking, lack of physical activity, and excessive alcohol use.

In 490 BC, the world's first marathon runner Pheidippides ran from Marathon to Sparta, and then to Athens to announce the Greeks had defeated the Persian army. This was about 150 miles in three days. Herodotus states Pheidippides first words on arrival were, "Joy to you, we've won." His next words were likely "My feet are killing me!" And they did; right then and there!

Why has it taken physicians over 2,500 years to understand that maximum physical exercise for very long periods of times are as unhealthy for their patients as was for Pheidippides? I don't know; it's all Greek to me.

References and Sources

Send request by e-mail to lfleenor@msma.org. **MM**



Let's Work To Keep Missouri From Going To Pot!

Let's Not Kid Ourselves About Marijuana

by Mitchell S. Rosenthal MD

Colorado makes pot legal, 'Rocky Mountain high' jokes follow. Now watch the tragedies start piling up.

Pot is always good for a giggle, and that makes it hard to take marijuana seriously. The news and entertainment media couldn't resist puns on "Rocky Mountain high" when Colorado started the year with legal sales of marijuana for recreational purposes. TV stations across the country featured chuckling coverage of long lines outside Denver's new state-licensed pot shops. Legalizing marijuana isn't just amusing. It's increasingly popular with legislators and the public. And why not? No matter how high stoners get, they're nowhere near as scary as out-of-control boozers, right? Stoners don't brawl in bars. They're not into domestic violence.

A Gallup poll last year found 58% of Americans favoring legalization (although other surveys report more slender majorities). Decriminalization of pot possession is widespread: 20 states sanction marijuana use for medical or quasi-medical reasons, and, following Colorado's and Washington's lead, proponents of legalization are targeting Alaska and Oregon for ballot initiatives in the near future, and six other states after that.

Yet marijuana is far from safe, despite the widespread effort to make it seem benign. Pot damages the heart and lungs, increases the incidence of anxiety, depression and schizophrenia, and it can trigger acute psychotic episodes. Many adults appear to be able to use marijuana with relatively little harm, but the same cannot be said of adolescents, who are about twice as likely as adults to become addicted to marijuana. The new Colorado law limits pot sales to people 21 or older, but making marijuana available for recreational use normalizes it in society. The drug will be made more easily available to those under 21, and how long until the age limit is dropped to 18?

Adolescents are vulnerable—and not just to pot. That's how they are programmed. They make rash and risky choices because their brains aren't fully developed. The part of the brain that censors dumb or dangerous behavior is last to come on line (generally not before the mid-20s). Meanwhile, the brain's pleasure-seeking structures are up and running strong by puberty. When you link adolescent pleasure-seeking and risk-taking to marijuana's impairment of perception and judgment, it isn't surprising that a 2004 study of seriously injured drivers in Maryland found half the teens tested positive for pot.

Marijuana impairs learning, judgment and memory—no small matters during the adolescent years—and it can do lasting harm to the brain. Dr. Nora Volkow, director of the National Institute on Drug Abuse, has found that marijuana can damage cognitive function in adolescents by disrupting the normal development of the white-matter that brain cells need to communicate with each other. Most disturbing is a discovery about marijuana last month at Northwestern University's Feinberg School of Medicine. Researchers there have found lasting changes in "working memory," brain structures critical to memory and reasoning. A source of ready recall for basic information, like telephone numbers, and solutions to everyday problems, working memory is also a strong predictor of academic achievement.

Dr. Volkow and most other experts are troubled by changing teen attitudes about marijuana. Barely 40% of adolescents now believe regular use is harmful—down from 80% two decades ago. Teen drinking and cigarette smoking have declined, and their abuse of prescription painkillers has fallen off sharply, but teen marijuana use continues to increase. The University of Michigan's Monitoring the Future survey last year found that more than 45% of high-school seniors have smoked pot and 6.5% now smoke it daily (a rate that has tripled over the past two decades). At the substance-abuse programs of Phoenix House, and at similar programs across the country, marijuana is the primary drug of abuse for close to 70% of teens in treatment.

No one can say how marijuana legalization will play out. A perception of legal marijuana as safe, combined with sophisticated marketing, may well double or triple pot use. Warning of aggressive promotion, drug-policy expert Mark Kleiman, who studied potential issues of a legal marijuana market for the Seattle City Council, pointed out last year: "The only way to sell a lot of pot is to create a lot of potheads."

As we learn more about the realities of legalizing recreational marijuana, I suspect pot won't seem so funny anymore. Remember, drunks used to be good for a laugh too. A hiccupping, stumbling tosspot was a staple of Hollywood's screwball comedies in the 1930s and '40s. Smoking cigarettes was considered cool. The reality of wrecked lives and ruined health eventually changed public perceptions of these addictions. Now marijuana is becoming more widely regarded as a harmless amusement. That's not funny, it's tragic.



Dr. Rosenthal is a child psychiatrist and the founder of the nonprofit substance-abuse treatment and prevention organization Phoenix House. *Reprinted with permission from the Wall Street Journal.* **MM**

Is Obesity A Disease or A Behavior Abnormality? Did the AMA Get It Right?

by Howard Rosen, MD

Many observers thought that "corpulency" was a disease in some, but not all cases, which could lead to increased morbidity and mortality.

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In June 2013, the American Medical Association (AMA) House of Delegates voted to recognize obesity as a disease state requiring treatment and prevention efforts. A number of other medical societies had sponsored a resolution to support this idea, including the American Association of Clinical Endocrinologists, the Endocrine Society, the American College of Cardiology, the American College of Surgeons, and the American Heart Association. The National Institutes of Health had declared obesity a disease in 1998 and the American Obesity Society did so in 2008. Because the AMA is thought of as the most influential medical association in the country, their statement is expected to have a significant influence on health care policy, through effects on insurers, industry, and lawmakers. The stated purpose for this decision is to improve research into the causes of obesity, leading to improvement in methods to prevent and treat it, ultimately improving patient health and outcomes. This decision would be expected to improve insurance coverage and reimbursement to providers for treating individuals with obesity. In addition, this change in public policy by the AMA supports the concept that obesity is a serious disease that requires treatment and also removes the stigma currently associated with obesity (i.e., it is not just a poor lifestyle choice).

The AMA decision is controversial, since the AMA's own Council on Science and Public Health in 2012 said that there was not sufficient data to support calling obesity a disease. In this article I will discuss some of the issues associated with this controversy, as well as what we know regarding the etiology of obesity. I will then return to the discussion of whether designating obesity as a disease is an appropriate decision.

Obesity as a Leading Heath Problem

According to the American Heart Association, obesity is found in almost one-third of U.S. adults and 17% of U.S. children ages 2 to 19. Worldwide it was estimated in 2010 that there are approximately 500 million obese people and another 1.4 billion who are overweight. The number of obese individuals is estimated to rise to 700 million by 2015.[1] Obesity is estimated to cause approximately 112,000 to 365,000 deaths per year. Its prevalence has increased since the 1970s in the U.S. (data from NHANES II and III) and in Europe.[2] This increase has occurred across every age group, sex, race, and smoking status.[3]



Advertisement showing young woman with package of Loring's Fat-Ten-U food tablets and package of Loring's Corpula, a fat-producting food. Circa 1895

Obesity is recognized as a significant public health hazard, as it increases the risks for multiple diseases, such as type II diabetes, cardiovascular disease, hyperlipidemia, hypertension, stroke, breast and colon cancer, and degenerative arthritis.[4] The cost of treating obesity related conditions are estimated to range from 147 to 210 billion dollars per year. It decreases quality of life, functional capacity, and increases morbidity and mortality. Treatment has been shown to reduce morbidity and mortality.[5] Therefore, preventing or treating obesity would be very beneficial on both an individual and societal basis.

One of the controversies regarding whether to define obesity as a disease is the fact that there is not agreement as to the definition of obesity. Obesity can be defined as an excess of body fat that leads to increased morbidity and mortality. From an epidemiological standpoint, it may be defined as a BMI of greater than or equal to 30 kg of body weight per meter squared.[2] This is a simple and easy to use calculation, as the data are readily available. The BMI is considered a marker for adiposity and is widely used to predict and evaluate disease risk. It is not an ideal measure, as it does not account for variations in body composition. Other methods to measure body fat and composition include waist circumference, skin fold thickness, waist to hip ratio, waist to height ratio, bioelectrical impedance, and dual energy X-ray absorptiometry. These metrics or techniques are not consistently available in all settings. In 2012 the AMA Council argued that the lack of a universally agreed upon metric limits the ability to define obesity as a disease and therefore, calling it a disease would not improve health outcomes.

Can Obesity Ever Be 'Healthy?'

It is known that some people with a BMI in the obese range are putatively 'healthy,' and some with a normal BMI have an excess of visceral body fat and are not healthy. There is also the "obesity paradox." It appears that some people with a BMI in the obese or overweight range have better short- and long-term health outcomes than those with a normal BMI. Research suggests that the "obesity paradox" may have been due, in part, to the level of physical fitness of the individual. Those persons with a higher fitness level have the more favorable prognosis.[6] A more recently study[7] provides evidence that the "obesity paradox" is not true. This meta-analysis investigated the association of BMI, metabolic status, and cardiovascular events and total mortality. The result of this study was that obese individuals, regardless of their metabolic status (healthy or unhealthy) were at increased risk for adverse health outcomes, when compared to individuals of normal weight. This risk was seen only in the studies with more than 10 years of follow-up.

This study, and the accompanying editorial,[8] support the concept that obesity increases risks for adverse health outcomes, and should be considered a disease. AACE[5] and others[9] argue that the epidemiologic evidence supports the association of excess body fat with risks for other primary diseases, such as diabetes, hypertension, hyperlipidemia, and coronary artery disease. The lack of a universal metric should not preclude calling obesity a disease.

Is Obesity a Disease?

A related and more challenging controversy is whether obesity meets the definition of a disease. To discuss this, we need to agree on the definition of a disease, which is not as obvious as it would seem. Historically, it has long been recognized that people who are overweight or obese were at higher risk of sudden death; this dates back to Hippocrates

Corpulent Quotes 1600s-1934

"Corpulency may be ranked amongst the diseases arriving from original imperfections in the functions of some of the organs, yet it must be admitted also, to be most intimately connected with our habits of life."
-Thomas Sydenham, 1624-1689

"Corpulency, when in an extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers."
-Malcolm Flemyng, 1760

"The only disease to be mentioned in this chapter, I have, with other nosologists, named Polysarda; and in English it maybe named Corpulency, or, more strictly Obesity…This corpulency or obesity, is in very different degrees in different persons, and is often considerable without being considered as a disease. There is, however, a certain degree of it, which will be generally allowed to be a disease; as, for example, when it renders persons, from a difficult respiration, uneasy in themselves, and, from the inability of exercise, unfit for discharging the duties of life to others: and for that reason I have given such a disease a place here."
-W. Cullen, 1808

over 2500 years ago. More recent historical comments, from 1600 through 1934, demonstrate that many observers thought that "corpulency" was a disease in some but not all cases, which could lead to increased morbidity and mortality in some cases.[9]

There is not one agreed upon definition of a disease. I have chosen several as representative examples. Kincaid[9] states that disease is deviation from species-typical functioning; disease is deviation from the average. In the evolutionary function view, disease occurs when an organ is not performing the job that allowed it to evolve by natural selection.

A more widely held definition is that of Heshka and Allison;[10] theirs is an extraction of four points common to definitions from multiple general language and medical dictionaries:

1) Disease is a condition of the body, its parts, organs, or systems or an alteration thereof.

2) It results from infection, parasites, nutritional, dietary, environmental, genetic, or other causes.

3) It has a characteristic, identifiable, marked group of signs or symptoms.

4) It deviates from normal structure or function (variously described as abnormal structure or function; incorrect function; impairment of normal state; interruption, disturbance, cessation, disorder, derangement of bodily or organ functions).

Definitions from the FDA in 1993, Downey and Conway (2001), and Rene (2004)[9] share some but not all of these criteria. In 2007, the AMA stated that criteria 1, 2, and 4 were necessary for a condition to be called a disease. At that time, it stated that obesity did not meet the criteria to be considered a disease.[9] Several of these authors, as well as the AMA Council in 2012, did not think obesity met the definition of a disease. Conversely, AACE, in a 2012 position statement, stated that obesity met these three conditions.[5] The AACE position probably stems from differences of opinion in the definition of a disease, how to apply those definitions, and which facts regarding obesity fit which definition. As there is no universally accepted definition of a disease, it is possible that one cannot have a scientific, definitive answer regarding obesity. The American Obesity Society[9] suggested that since there is no clear definition of a disease, it does not make sense to ask if obesity is a disease. They do support calling obesity a disease based on a utilitarian approach to public health.

The epidemic of obesity and its associated complications are challenging the world's health care system and might slow or even reverse the life expectancy gains of the last 50 years. Understanding its multiple causes would help in the development of effective preventions and treatments. Obesity is a complex condition with many causes. In general, obesity results from an imbalance between energy consumption (dietary intake) relative to energy expenditure (energy used in metabolic and physical activity). People gain weight because energy intake exceeds expenditure, i.e., positive energy balance. There are multiple potential contributing factors to this imbalance including genetic, environmental, behavioral,

Corpulent Quotes 1600s-1934

"Fat is, of all the humors or substances forming part of the human body, the most diffused; a certain proportion of it is indicative of health, and denotes being in good condition – nay, is even conducive to beauty; but when in excess – amounting to what may be termed OBESITY – it is not only in itself a disease, but may be the cause of many fatal effects, particularly in acute disorders."
-W. Wadd, 1810

"Corpulency, when it arrives at a certain height, becomes an absolute disease."
-Robert Thomas, 1811

"That many persons never become corpulent, no matter what they may eat, is undoubtedly true. These remarks are not for them but for those whose habits of living have produced that degree of obesity which if it does not render life a burden, begets in him who is afflicted with it (for it is almost a disease) a state extremely uncomfortable, sometimes painful, and always mortifying."
-E. Price, 1867

"Obesity in man is often an infirmity, and sometimes a grave disease."
-Anonymous, 1886

"The accumulation of fat in the tissues, or obesity, is a pathological or diseased condition."
-Wood, 1893

"Obesity is not itself a disease in all instances."
-W.G. Campbell, FDA Chief, 1935

physiologic, psychological, social, and economic.[3]

Twin and adoption studies show that variations in BMI have a significant genetic component, and it has been estimated that these genetic effects contribute as much as 70% of the variation in obesity. These effects may contribute to obesity via effects on energy intake, expenditure, and abnormal regulation of satiety signals.[1] Rare, simple genetic defects such as leptin deficiency or MC4R abnormalities have clearly been shown to cause obesity. More common gene variations seem to have a small effect size on weight, and no single widespread gene has been found that can explain obesity. It is likely that multiple genes are involved in the heritability and susceptibility for obesity.[1, 11, 12]

Why is Obesity More Prevalent?

Environmental influences are another major contributor to obesity.[3,11,12,13] The so-called "obesogenic" environment with its reduced food costs, the especially plentiful high calorie dense foods, larger serving portions, reduced physical activity, and the influential food industry, are likely contributors. U.S. government food policies in the 1970s are also thought to be a contributor to obesity. Other environmental contributors include endocrine disrupters (industrially produced chemicals such as plastics) that can disturb endocrine function. The most widely studied of these is bisphenol A. Sleep deprivation, medications, social networks, stress, and changes in bacteria in the GI tract (microbiome) are thought to be contributing factors. It has been suggested that obesity is a biologic adaptation to this obesogenic environment,[14] or that it is a chronic relapsing neurochemical disease.[15] Epigenetics has been proposed as a possible link between the complex interplay of both genetic and environmental factors in regulation of energy intake, expenditure, and energy balance. [16]

There are multiple contributing factors for obesity, as well as many unanswered questions. If the environment promotes obesity, why is everyone not obese? Why do some people eat more than others? It is known that simply trying to increase calorie expenditure as a method of weight reduction does not consistently work. Studies have shown that losing fat mass can have adverse effects on appetite control and even reduce energy expenditures, making further weight loss even more difficult.[14] The contrarian food writer, G. Taubes,[17] as well as Hebert,[6] think that the energy balance hypothesis is incorrect, and that this has adversely influenced research and policy decisions on prevention, treatment, and public health. Both suggest further research into the causes of obesity.

What Good or Bad Effects Might Come From Calling Obesity a Disease?

So is it a good idea to label obesity a disease? Overall, I think yes it is despite the many controversies associated with the disease designation. These include the controversy regarding the lack of a universal definition for obesity, and whether it fits the scientific definition of a disease. There are

also concerns that the definition of obesity as a disease will shift the emphasis towards treatment with surgery/medications, and away from prevention efforts via lifestyle changes, including behavior modification, diet, and exercise. There are concerns that obese people will be labeled as having a disease, even if they are not sick. This could have effects on obese individuals' efforts to manage their weight and make lifestyle changes.

The position of the AMA, AACE, Obesity Society, and other medical organizations is that obesity and its related diseases have a significant adverse effect on public health. This designation will focus society on the importance of preventing and treating it. A designation of obesity as a disease that results from a complex interplay of behavioral, environmental, and genetic factors should shift the stigma and discrimination from considering it as simply a lifestyle issue of poor eating habits and sedentary lifestyle.

In our society, labeling it as a disease would be expected to improve attitudes and financial support for obesity treatment. This would include more resources for health promotion, research into the behavioral, environmental, and genetic causes, as well as prevention and treatment (medical and surgical). This would improve insurance coverage and reimbursement for screening, health promotion, prevention, and treatment.

Obviously obesity is a complex topic. Despite extensive research, the causes for this disease are not well understood and good treatment options remain elusive. As Dr. George Bray, a distinguished obesity researcher, once said, "Obesity isn't rocket science, it's much more complicated."[13]

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The Medicare Advantage Debacle

by Arthur Gale, MD

On October 2, 2013 Jenny Hayhurst, Vice President, Network Management, UnitedHealthcare, the country's largest health insurance company, sent a letter to thousands of physicians, a portion of which appears below.

CERTIFIED MAIL, RETURN RECEIPT REQUESTED
Re: Notice of Amendment to the Contract

Dear (Doctor):

Given the significant changes and pressures in the health care environment, we have undertaken a review of our network and making changes as to its composition. As a result, **UnitedHealthcare is amending your Agreement referenced above to discontinue your participation in the Medicare Advantage network effective on February 1, 2014."**

Bold type is present in the original letter[1]

This termination letter was sent to thousands of doctors in at least 10 states. Among the practices that were dropped are the Yale Medical Group which includes 1200 faculty physicians and the well respected Moffitt Cancer Center in Tampa Florida.[2] In Ohio the cancellations included most of the orthopedic surgeons in Dayton, the only hand specialists in the Cincinnati area, and a large gastroenterology group that provides most of the inpatient care at five Cincinnati hospitals.[3]

The American Medical Association, forty three national specialty societies, forty state medical association, and several states attorney generals quickly reacted. They wrote a joint letter to Marilyn Tavener, the head of the Centers for Medicare and Medicaid Services complaining about the abrupt dismissals of thousands of physicians.[4] The Connecticut State Medical Association supported by the Litigation Center of the AMA successfully filed suit and obtained a permanent injunction from a federal judge placing the actual dismissal of doctors on hold. This is where things stand at the time of this writing. The two parties in the dispute are trying to seek a compromise.[5]

The primary cause of the problem is that Medicare as part of the Affordable Care Act is beginning to cut back on its huge subsidy to Medicare Advantage. Currently Medicare Advantage costs taxpayers between fourteen and sixteen percent more than standard Fee for Service (FFS) Medicare. This subsidy amounted to roughly $14 billion in 2009. HMOs are supposed to cut costs. Yet Medicare Advantage requires huge subsidies in order to survive. The government plans to save $156 billion over the next decade by cutting back on the Medicare Advantage subsidy until it reaches financial parity with standard Medicare FFS.[6]

Medicare Advantage is an HMO. Members of Medicare Advantage do not have to buy supplemental insurance like they do in Standard Fee For Service (FFS) plans. They also get other extra benefits like eyeglasses and gym memberships. Some Medicare Advantage plans also offer free drugs to



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its members. Medicare HMOs were created in 1973 under the Nixon administration with support of both political parties. Initially these plans were called Medicare Plus Choice. At the time many experts thought that HMOs would lower health care costs. Other more realistic entrepreneurs believed they could be quite profitable. However, in the beginning no one thought that Medicare HMOs would actually be more expensive than standard FFS Medicare. It never made any sense that the federal government would pay more for one set of Medicare beneficiaries that another. Yet that is exactly what has happened.

One research group estimated that subsidies to Medicare HMOs over the past three decades have cost the taxpayer $282 billion.[7] Although Medicare Advantage has been a drain on our government it has been a boon to the health insurance industry. It has become the most profitable product of health insurance companies like UnitedHealthcare and Humana. And now the insurance companies are fighting ferociously to keep it that way.

They have embarked on a mass advertising campaign in an effort to convince the public that the government is taking away their $156 billion benefit.[8] They refer to this cut as a theft by the government when in reality it is simply the removal of an unnecessary and unfair subsidy and a flagrant example of corporate welfare. The health insurance lobby has recruited hundreds of thousands of senior citizens to write letters to Congress not to defund Medicare Advantage. Congress finds itself in a difficult position. Those senators and representatives who have demanded fiscal austerity by cutting back on Medicare expenditures are the same ones who are beholden the health insurance industry for huge campaign contributions.

And now Medicare Advantage has found a scapegoat to blame for the high cost of Medicare Advantage-physicians. In a page out of George Orwell's book 1984 they are dropping doctors who take care of the sickest patients claiming that they are not practicing "quality" medicine.

Medicare Advantage has become a victim of its own successful advertising campaigns. Its membership now accounts for about 28% of all Medicare patients. In some areas of the country this number has risen to over 40%.[9] With all these new patients however, Medicare Advantage must now assume the financial responsibility for the many chronically ill, more costly patients whom it has enticed into its plans.

To illustrate this point I will cite a recent personal experience. A patient, whom I had treated for over three decades, entered the hospital on January 1, 2014 under my name but who, unbeknownst had switched to a Medicare Advantage plan. She has multiple medical problems including severe congestive heart failure with an ejection fraction of 15% and an automatic internal defibrillator. She had broken her hip. Her son told me "she had to switch", which I interpret as meaning she could no longer afford standard Medicare FFS. She was hospitalized almost one month most of which was spent in the intensive care unit. Her hospital bill was most likely in the six figure range.

Instead of admitting that it has no magic wand for lowering the costs of caring for chronic seriously ill patients like the one I just cited Medicare Advantage instead accuses physicians of not practicing "quality" medicine. Medicare Advantage and all HMOs for that matter have always profited by avoiding sick patients and skimming off the healthiest patients.[10]

The one positive that may emerge from the firing of thousands of doctors is that it finally focuses a spotlight on the practices of Medicare Advantage. By mobilizing medical associations, the judiciary, states' attorney generals and the public especially those who have to scurry about to find new doctors. Medicare Advantage is no longer able to escape scrutiny. It can no longer deceive the public with its misleading advertising and false promises.

What is needed is an open public discussion with complete transparency from all parties. After all it is the beleaguered taxpayer who footing the bill for an essentially useless programs like Medicare Advantage whose main beneficiaries are insurance companies. This public discussion is just beginning. Recently the respected magazine Bloomberg's Business Week has come out for reining in Medicare Advantage subsidies.[11] As Supreme Court Justice Louis Brandeis said, "A little sunlight is the best disinfectant." When citizens are able to sift the facts and weigh the evidence they may conclude that it is in their best interests to eliminate Medicare Advantage rather than physicians.

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PERSPECTIVE

The Death of the Bedside Manner: ObamaCare is Speeding the Decline in the Quality of Medical Practice

by Marc K. Siegel, MD

How can ObamaCare be labeled a success when it adds layers of bureaucracy to an already overburdened system?

'It is as painful perhaps to be awakened from a vision as to be born," James Joyce wrote famously in his masterpiece "Ulysses." I recently had such an experience when my office manager—who protects me from the daily insurance grind of referrals and approvals and pre-certifications and blood drawing—was out sick. Thus the veil was lifted from my eyes, and I awoke to the harsh realities of our medical future. One patient was severely depressed and needed medication and a referral to a psychiatrist. Another was having trouble breathing from asthma that requires inhalers. A third had a faded rash on her arm that she was ready to call a spider bite until she showed me a two-day-old iPhone photo. It was the angry red rash of Lyme disease. Each problem had an effective treatment but each visit took over half an hour to carefully complete. The appointments were gratifying, in an old-fashioned way. Patients still have the expectation that their doctor will be patient and listen carefully, but one by one doctors and patients are awakening from that comforting vision of the past to the rushed, restricted world of the ObamaCare future. Thanks to that eye-opening week without my office manager, when I ran hours behind, I was forced to forfeit the vision I had of myself as an old country doctor practicing in a big city.

For me and many of my colleagues, the real practice of medicine is supposed to involve an intimate encounter with each patient and a diagnosis of illness leading to a potential cure. In the future, however, a diagnosis of Lyme disease or the severity of a patient's depression may be missed because showing the photo or taking an extensive mental-health history doesn't fit squarely into the 10-minute visit authorized by insurance, along with mandatory computer documentation, insurance verifications and appointment scheduling. These problems predate ObamaCare, but the new law brings more regulations and low-quality insurance at a time when we are already struggling to comply with the electronic health-record mandate.

Supporters of health reform will say that the Affordable Care Act didn't cause all these problems, that President Obama shouldn't be blamed for wanting to make sure that everyone has health insurance. Unfortunately, the kind of insurance that is growing under ObamaCare's fertilizer is the exact kind that was jeopardizing the quality of health care in the first place: the kind that pays for seeing a doctor when you are well, but where guidelines and regulations predominate and choice is restricted when you are seriously ill. How can quality of care not be affected if the antibiotic or statin drug or MRI scan I feel you need isn't covered under your plan? How can ObamaCare be labeled a success when it adds

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layers of bureaucracy to an already overburdened system?

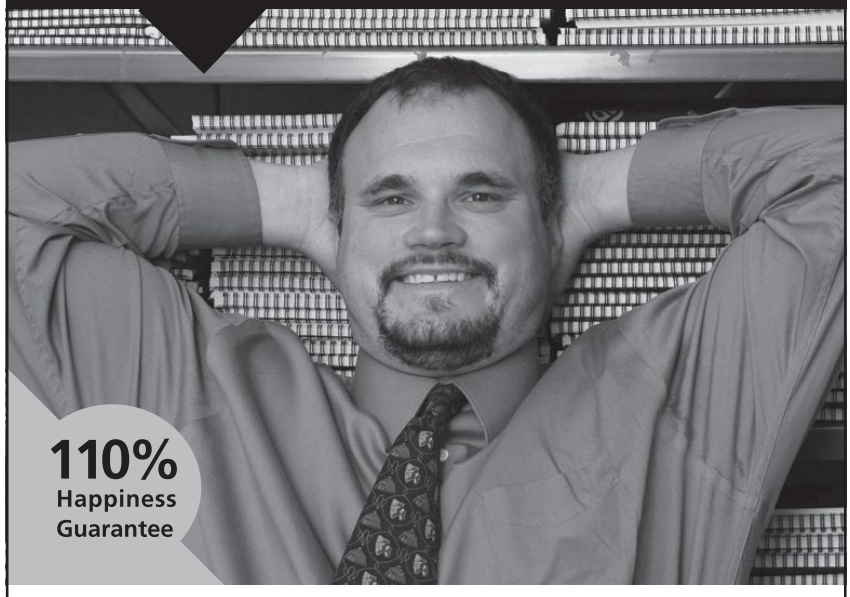
This month, even as Health and Human Services struggles to fix the health-exchange websites, the Obama administration announced that errors are occurring on the back end between the government and insurers at a rate of one out of four enrollees. This means that when you come to see me in January, assuming I actually participate in your narrow new ObamaCare network, there is a substantial chance you will never make it past the front desk because your new insurance will not be active. Since insurers are being compelled to cover more folks with pre-existing conditions, with no lifetime limits, and to cover everyone in a family plan at least up to the age of 26—all popular provisions of the ACA—they reduce costs by cutting fees to vulnerable doctors while restricting the tests they can order. This makes the practice of quality medicine almost impossible, but it helps preserve an insurance company's bottom line while complying with a government mandate. That copay that you no longer have to pay for colonoscopies or mammograms may have been the one bit of steady cash keeping in business many physicians and providers who perform them but work on very thin profit margins.

What should have been done? If the government felt that a significant segment of the population was underserved, they should have hired the doctors to serve them and built the clinics to serve them in—and mandated the scaled back, affordable insurance that covers severe illness only.

What ObamaCare gave us instead is a hybrid that should make both Democrats and Republicans, doctors and patients unhappy: big business combined with big government. **MM**

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The Nobel Path of Cellular Proteins

by Joel C. Eissenberg, PhD & William S. Sly, MD



"We are seeing cells more and more clearly as chemical factories, where the various products are manufactured in separate workshops . . ."

-Eduard Buchner, 1907 Nobel Lecture

Right: Portrait of Alfred Nobel



2013 Nobel Laureates in Physiology or Medicine
From left: James Rothman, PhD,
Randy Schekman, PhD &Thomas Südhof, MD.[17]



Joel C. Eissenberg, PhD, (left) is a Professor and Associate Dean for Research, and William S. Sly, MD, is a Professor and the James B. and Joan C. Peter Endowed Chair in Biochemistry & Molecular Biology, Edward A. Doisy Department of Biochemistry and Molecular Biology, Saint Louis University School of Medicine.
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Abstract

For one week every October, the world awaits the Nobel Prize announcements. While much publicity is focused on the laureates, the awards in the sciences also recognize high-impact fields of research. The 2013 Nobel Prize in Physiology or Medicine honored three scientists whose research defined the mechanisms by which cellular vesicles sort proteins to their final destinations. This research shaped a modern understanding of how protein sorting controls cellular identity and function.

Introduction

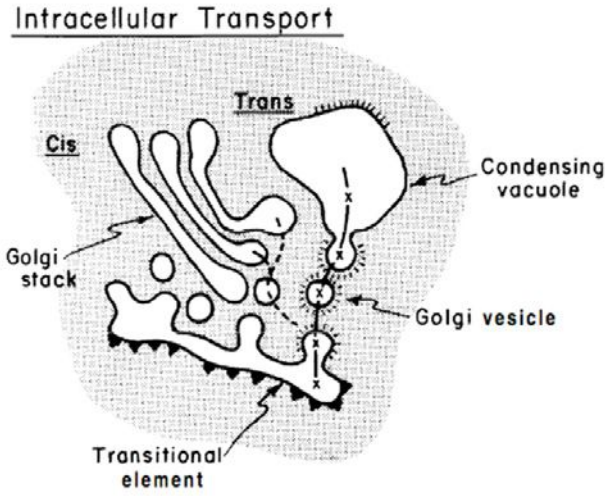
Alfred Nobel (1833–1896) was a brilliant Swedish engineer who amassed a fortune from his many patents, the most profitable of which was that for the invention of dynamite. He bequeathed over 90% of his assets to create a series of prizes for "those who confer the greatest benefit on mankind" in physics, chemistry, peace, philosophy, and literature. The 2013 Nobel Prize in Physiology or Medicine honored three exceptionally innovative scientists, Drs. James Rothman, Randy Schekman and Thomas Südhof . Their research defined mechanisms by which intracellular membrane transport vesicles are formed, loaded with cargo of specific proteins, and then deliver their contents by membrane fusion to other compartments or to the plasma membrane for secretion. This system allows the cell to sort the various newly synthesized cargo proteins to their final destinations under precise control. Not only did this research shape our modern understanding of how protein sorting controls cellular identity

and function, it also has medical relevance. We now know that disturbances in this transport system have deleterious effects that can contribute to neurologic diseases, including autism and schizophrenia, as well as to diabetes, hematological and immunological disorders.

Cell biology was born in the 17th century with the invention and application of light microscopes to living and fixed cells and tissues. Most of the cellular structures we know today were identified and named by the early 20th century, although their functions weren't fully understood. Linking cellular form to function is the "holy Grail" of modern cell biology. Key advances were made during the mid-1900s through the application of biochemistry to dissect and characterize the various visible organelles and the invisible macromolecules they contain that guide essential cellular functions. The initial fruits of the histology/biochemistry synthesis were recognized with the award of the 1974 Nobel Prize in Physiology or Medicine to Albert Claude, Christian de Duve and George Palade. The basic outline by which proteins traveling in cell organelles are sorted, as understood in 1974, is cartooned in Figure 1. While this level of understanding was extolled in the recognition given these three awardees, it was still quite primitive. Filling in the molecular details took another 40 years.

The research campaigns that resulted in the 2013 Nobel Prize in Physiology or Medicine were pursued on three fronts, using three different strategies that eventually converged on a common basis for understanding key mechanistic features of "the machinery regulating vesicle traffic." In the sections that follow, we summarize the exciting revelations recognized by the 2013 prize, the distinct paths taken by each of the 2013 laureates, and the implications of this work for science and medicine.

Figure 1
1974 view of intracellular protein transport. "Cis" and "Trans" refer to the outer compartments of the Golgi stack. In this cartoon, vesicles are depicted as small circles that bud from the surface of the rough endoplasmic reticulum ("Transitional element").
From: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1974/palade-lecture.pdf



Cargo Delivery in the Cell

All cellular proteins are synthesized in the cell cytoplasm on the same factory platforms, called ribosomes. For proteins that need to be segregated into subcellular compartments (called "organelles") such as lysosomes, or to be sent to the cell surface as pore-forming proteins, receptors or secreted proteins, each ribosome producing one of these proteins first becomes anchored to the surface of a membrane-bound tubular network called the endoplasmic reticulum (ER) into which the newly formed protein is injected or "translocated." Defining the process by which this translocation is achieved lead to the 1999 Nobel Prize in Physiology or Medicine for Dr. Gunter Blobel. From this point, the proteins are trafficked into and through a series of stacked membrane pouches called the Golgi complex (named after the 1906 Nobel Laureate Camillo Golgi) via small, membrane-bound spheres, called "vesicles," of about 50 nm in diameter. Along the way, many proteins become modified by the addition of sugar –containing side chains by enzymes in successive Golgi compartments. At the end of their journey through the Golgi stack, the proteins are again packaged into small vesicles that bud from the Golgi membrane surface and then move to other intracellular compartments such as lysosomes or to the plasma membrane for secretion.

While such transport vesicles are found in the cytoplasm of all eukaryotic cells, the cargo these vesicles contain can vary widely, even in the same cells. How vesicles are formed at the surfaces of various cell membranes, how their individual cargoes are allocated to specific vesicles, and how vesicles are sorted to destinations appropriate to their cargo are all fundamental to understanding cellular identity and function. The 2013 Nobel Prize in Physiology or Medicine to Drs. Rothman, Schekman and Südhof recognized the major advances these investigators and their research teams made in our understanding of vesicle formation, sorting and delivery. While our understanding of these processes was influenced by the findings of hundreds of researchers, the Nobel Prize

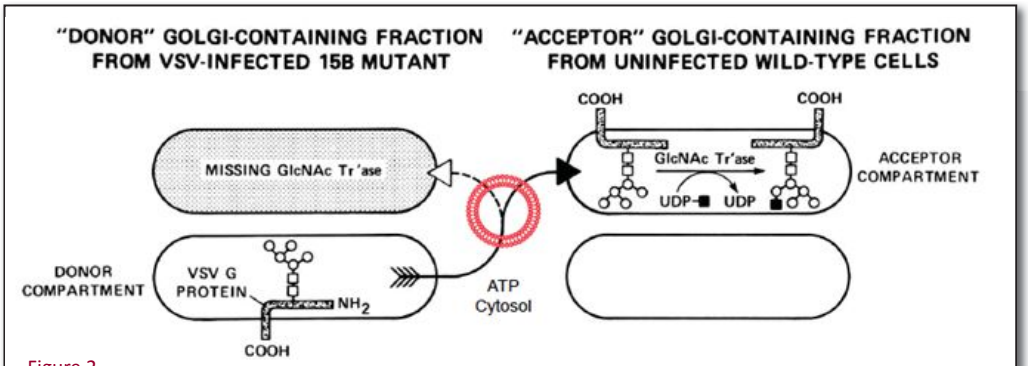


Figure 2
Cartoon of the assay used by the Rothman lab to detect vesicle-mediated transport between two Golgi compartments. The "Donor Compartment" consists of Golgi taken from cells defective in the protein-modifying enzyme N-acetylglucosamineyltransferase but containing the membrane-bound vesicular stomatitis virus G (VSV G) protein. The "Acceptor Compartment" consists of Golgi taken from cells that express N-acetylglucosamineyltransferase but not viral protein. The assay consists of detecting the modification of the VSV G protein by the transferase enzyme, which can only occur via vesicles (red ring) that carry the VSV-G protein from the Donor to the Acceptor compartment in the presence of the energy-providing molecule ATP and components found in added cellular cytosol.
From Balch et al., 1984.

can be awarded to a maximum of three individuals. Few would dispute the selection of these three awardees as the ones who made the most significant contributions to this field of cell biology.

Three Different Paths to the Nobel Prize

Dr. James Rothman and his team chose the pathway of biochemistry. They developed a novel and powerful cell-free biochemical approach to define the molecules in mammalian cells required to recognize and sort vesicles to their intermediate destinations. To do so, they exploited observations by prior workers indicating that some newly made viral proteins use the cell's natural sorting system to gain access to the host cell surface following infection. Along the way, these viral proteins undergo the same modifications, including addition of sugar containing side-chains, that the normal host cell proteins undergo en route to the plasma membrane. As tools, they chose a well-characterized virus to infect well-characterized mutant cells lacking a specific Golgi enzyme required for a particular viral protein modification (a particular sugar addition to its oligosaccharide side chain), without which the chain would fail to be completed. The Golgi membrane vesicles were purified from these cells following infection. Next, they mixed these "donor" Golgi in a test tube with Golgi prepared from normal cells and asked which normal cell components were required for transfer of the viral protein from donor Golgi to the normal "acceptor" Golgi where the appropriate modification of the viral protein could be made (See Figure 2).

These experiments—and others building on them—eventually allowed Rothman and his colleagues to define key steps in the mechanism driving vesicular transport in mammalian cells.

The Schekman team took a genetic approach to analyze the mechanism of vesicle trafficking, using the budding yeast, which is ideally suited for genetic manipulation, as their model organism (Schekman, 2002). They set out to develop genetic screens to isolate yeast cell mutants defective in each of the steps in the secretory pathway. In one strategy, they took advantage of the observation that yeast defective in any step of sorting accumulate secreted proteins and vesicles, causing an increase in buoyant density. Mutants identified by the strategy turned out to have different defects in processing and secretion all along the partway (endoplasmic reticulum, Golgi and vesicle sorting from the Golgi). The different mutations, called "sec" mutations for secretion-defective, were characterized and eventually cloned. The normal product of each mutant gene was found to be required for one step in the trafficking of vesicles within the cell. This and other innovative genetic screens eventually identified over fifty genes whose products are required for trafficking of secreted proteins from the ER to the Golgi, from the Golgi to other intracellular compartments, and from the Golgi to the plasma membrane (See Figure 3). Importantly, several of the yeast genes uncovered by the genetic screens turned out to encode proteins that were closely related to those reported by the Rothman lab to be key in mammalian vesicle sorting. Thus, many components of the transport pathway were highly conserved evolutionarily. Additional genetic studies disclosed a temporal sequence of gene activity that mirrored the pathway followed by secretory proteins in pancreatic cells, providing further support for the evolutionary conservation of the entire secretory process. Indeed, this extensive conservation allowed workers in mammalian systems to exploit the

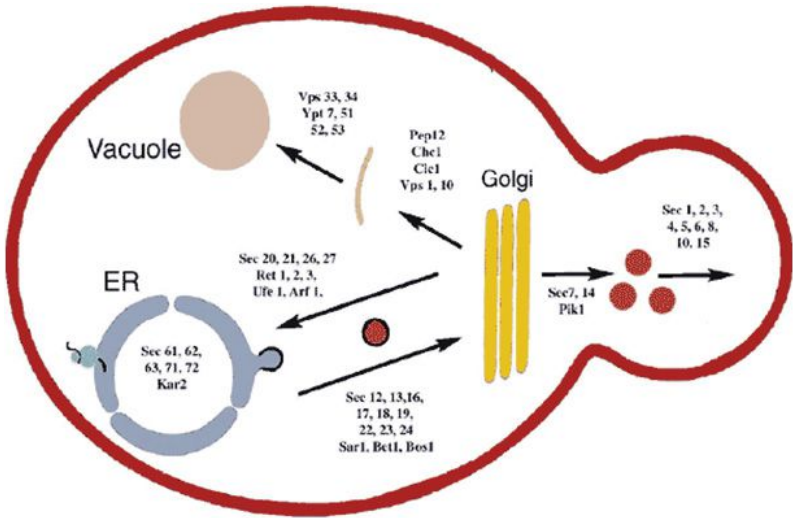


Figure 3
Cartoon showing the yeast secretory pathway. A red outline depicts a yeast cell and a growing bud to the right. Vesicles shuttle bi-directionally between the ER (blue) and the Golgi (yellow), while other vesicles target the yeast vacuole (pink) or the plasma membrane of the growing yeast bud. Arrows are labeled with the names of yeast genes encoding proteins that control vesicle trafficking at the indicated steps.
From Schekman, 2002.

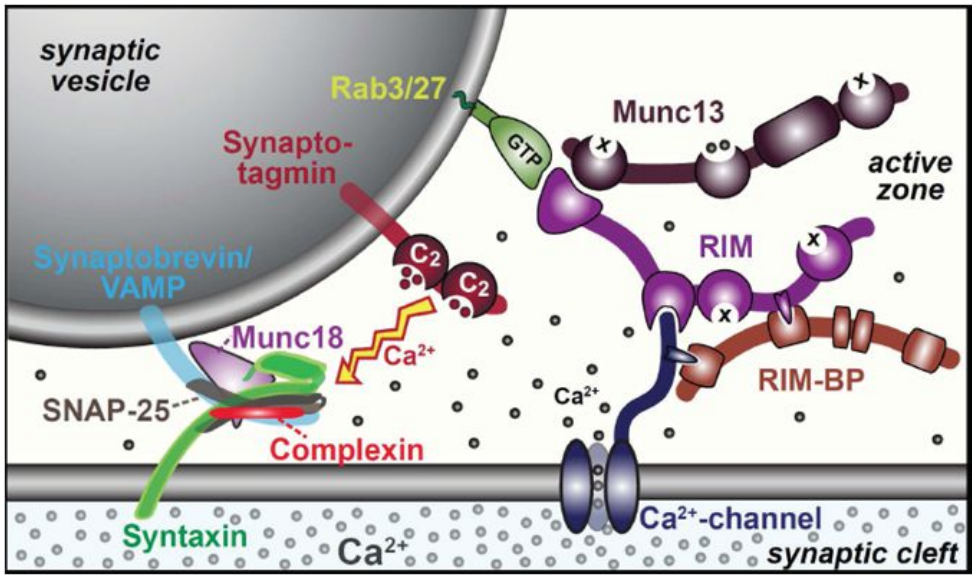


Figure 4
Mechanism linking calcium channels, calcium ion influx and synaptic vesicle fusion to the plasma membrane at the synaptic cleft. A calcium channel is physically tethered to a nearby synaptic vesicle via the RIM/RIM-BP/Munc13 protein complex bound to the Rab3/27 protein-Guanosine-triphosphosphate (GTP). Thus, when the calcium channel opens as a result of a nerve impulse, incoming calcium is bound by domains ("C2") on the vesicle membrane protein synaptotagmin, which triggers an interactions with the Synaptobrevin/VAMP/Munc18/SNAP-25/ Complexin/Syntaxin complex to dock the synaptic vesicle on the plasma membrane, releasing the neurotransmitters in the vesicle to the synaptic cleft.
From: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2013/sudhof-lecture.html

genetic information from yeast in identifying and characterizing additional components of the mammalian transport system.

Südhof and his colleagues began with the goal of understanding events related to synaptic transmission at presynaptic nerve termini. Since neuronal signal transmission depends on storage of neutotransmitters in vesicles just below the plasma membrane at nerve termini and on regulated release of the presynaptic vesicle contents, it was perhaps foreseeable that a confluence would be uncovered between synaptic events (the rapid synaptic vesicle release at nerve termini following stimulation and slower subsequent membrane retrieval in endocytic vesicles) and other vesicle-mediated mechanisms. Their studies built on previously identified targets of the tetanus and botulism neurotoxins, which had identified calcium-dependent membrane-binding proteins. The neurotoxin targets turned out to be subunits of the same complex described by the Rothman lab as critical for vesicle fusion to membranes. In additional important biochemical experiments, the Südhof lab indentified another key protein—called Munc18 in mammals—that binds this complex, a protein independently identified in the Schekman lab as essential for secretion in yeast. Ultimately, they showed that core factors that facilitate fusion vesicle fusion

to the plasma membrane also link vesicle-membrane fusion to the response to calcium channel opening triggered by nerve impulses. A similar mechanism is shared by vesicle trafficking in the mammalian Golgi and in vesicle-mediated protein secretion in yeast (See Figure 4).

Thus, the work of the three 2013 Nobel laureates converged and illuminated a highly conserved fundamental mechanism that governs vesicular trafficking in diverse cell types and can subserve diverse functions. How important is the "secretory pathway?" Well, more than one third of the human genome encodes proteins that must traverse the secretory pathway. That's huge! To encapsulate why this transport mechanism is so important to our cells and to those of all organisms (and to the Nobel Committee), the Nobel Foundation stated: "Without this wonderfully precise organization, the cell would lapse into chaos."

Medical Implications of the 2013 Nobel Prize in Physiology or Medicine

Given the fundamental role played by vesicle trafficking in both general and specialized cell functions, it is perhaps not surprising that mutations affecting key proteins in the pathways discovered by the 2013 Nobel laureates have been uncovered in association with disease syndromes. We now know that disturbances in this transport system have deleterious effects that can contribute to neurologic diseases including autism (Castermans et al., 2010) and schizophrenia (Johnson et al., 2008), as well as to diabetes (Bogan, 2012), immunologic (Janka, 2012) and hematologic disorders (Khoriaty et al., 2012). The Schekman lab has been characterizing human diseases that arise from secretory pathway problems. He has identified the structural basis for a rare human disease that disrupts the construction of a coat protein complex essential for transport vesicle formation in yeast. He is also studying whether roadblocks in the secretory pathway contribute to the accumulation of protein amyloid in the brains of Alzheimer patients. Südhof has extended his studies to presynaptic proteins (neurexins) and post-synaptic proteins (neuroligins) that bind to each other across synapses. Alterations in these proteins disturb brain chemistry and have been implicated by genetic studies in some cases of schizophrenia and autism.

Some examples of human diseases that have been linked to defects in specific vesicular trafficking proteins follow.

- Ohtahara Syndrome and West Syndrome are progressive encephalopathies of newborns, characterized by epileptic seizures. The genetics of these disorders are complex, but among the genes implicated is the gene encoding Munc18 (Otsuka et al., 2010; Saitsu et al., 2012), a protein shown by the Südhof lab to be important in tethering neurotransmitter vesicles to the synaptic cleft in neurons (See Figure 4).

- Alpha-synuclein is an abundant brain protein that is critical to the delivery of neurotransmitter-bearing vesicles to the pre-synaptic terminals of neurons. Alpha-synuclein aggregates accumulate in the brains of Parkinson's Disease patients (Iwatsubo, 2003). Mutations in alpha-synuclein have been found in some pedigrees of familial Parkinson's Disease (Iwatsubo, 2003), and loss of alpha-synuclein in mice promotes neurodegeneration (Burré et al., 2010). These findings are consistent with a model in which alpha-synuclein aggregation sequesters the protein from its normal sites of activity equivalent to an inactivating mutation.

- The mechanistic explanation Familial Hemophagocytic Lymphohistiocytosis is a rare blood disorder characterized by anemia, hemophilia, hyperactivation of the immune system, neurological problems and increased cancer risk. Mutations in Unc13D result in Familial Hemophagocytic Lymphohistiocytosis Type 5 (zur Stadt et al., 2009), while mutations in the gene encoding syntaxin 11 result in Familial Hemophagocytic Lymphohistiocytosis Type 4 (zur Stadt et al., 2005). In both cases, the affected proteins are key players in vesicle trafficking (See Figure 4). The mvechanistic explanation for how lesions in these genes account for the clinical presentation remains elusive.

- Patients with Congenital Dyserythropoietic Anemia Type II suffer from progressive splenomegaly, gallstones and iron overload. The disorder is associated with mutations in the Sec23b gene (Schwarz et al., 2009). Sec23b

encodes a protein related to the yeast Sec23 protein, which the Schekman lab showed is required for the transport of vesicles from the endoplasmic reticulum, where secreted proteins originate, to the Golgi apparatus, where the proteins are modified in preparation for secretion (See Figure 3). Why would loss of such a basic function have such a selective effect on hematopoiesis in humans? The answer probably lies in the fact that humans express two closely related forms of Sec23, Sec23a and Sec23b. During erythroid differentiation, Sec23b is induced to high levels, making it the dominant form in these cells. Presumably, the remaining Sec23a in patient erythroid cells is insufficient to support normal red cell proliferation.

- Anderson Disease, Chylomicron Retention Disease (CMRD) and CMRD with the Marinesco–Sjogren Syndrome are inherited pediatric disorders characterized by deficiency in fat-soluble vitamins, low serum cholesterol and selective absence of blood chylomicrons. Mutations in the SARA2 gene are associated with each of these diseases (Jones et al., 2003). SARA2 encodes one of a family of protein related to the yeast Sar1, also required for transport of vesicles from the endoplasmic reticulum to the Golgi (See Figure 3).

It seems likely that additional examples of disorders resulting from defects in vesicle sorting will emerge as the genetic bases for single-gene syndromes are discovered. These, in turn, may point to milder, non-syndromic mutations that could influence progression of other diseases. Importantly, for clinical medicine in the future, a mechanistic understanding of each of these may point the way to novel therapies.

Summary and Future Prospects

In his Nobel lecture, Hugo Theorell defined the ultimate goal of enzyme research as "filling of the yawning gulf between biochemistry and morphology," (Theorell, 1955) by which he meant a mechanistic understanding of how form (cell, tissue and organ histology) follows function (the specific activities of proteins and other macromolecules) in the body. The work of the 2013 Nobel laureates, their many associates and others whose work contributed to the field, have brought us closer to this goal. Outstanding questions include: do vesicles simply randomly diffuse to reach their targets, or are they actively transported along intracellular 'ziplines?" How are vesicles properly sorted according to their contents and how are errors in sorting avoided?

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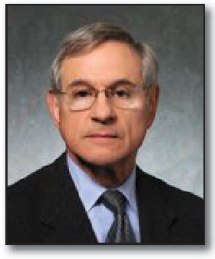
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Getting Comfortable With Death

The Culture Change of Life & Death: Will Health Reform, Demographics & the Economy Bring It About?

by Harvey Tettlebaum, JD & J. Andrew Billings, MD

Studies have shown that palliative care patients have a higher quality of life, and lower depression rates at twelve weeks after diagnosis, use less aggressive care, use more hospice care, and live longer after diagnosis.



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It is the twentieth anniversary of the enactment of the Patient Self Determination Act (PSDA), which is part of the Omnibus Budget Reconciliation Act of 1990[1]. It applies to hospitals, nursing facilities, home health agencies and hospice programs, and other organizations and requires information to be provided to persons receiving care from providers about their rights under state law, whether statutory or case law, to allow them to make decisions concerning their medical care including their right to accept or refuse medical or surgical treatment and the right to formulate advance directives. It also contains other provisions regarding the documentation of compliance with the statute by the organizations involved. It was designed, in part, to give patients the right to refuse treatment and to designate their wishes in advance to avoid the situations such as arose with Nancy Cruzan and Terri Schiavo. If its success is measured by the number of Americans who have advance directives, then it has not accomplished its goal completely.[2]

More recently, in 2009, the Congress proposed §1233 of the Health Care Reform legislation to require practitioners to provide information about certain items to their patients which, not unlike the PSDA, required an explanation of advance directives, health care proxies and advance care planning but also information regarding palliative care. Section 1233 further required advance care planning consultations in certain situations including "diagnosis of a chronic, progressive, life-limiting disease, a life-threatening or terminal diagnosis or life-threatening injury, or upon admission to a skilled nursing facility, a long-term care facility, or a hospice program." It further provided for development during that consultation of orders "regarding life sustaining treatment" to enable the patient to provide his or her preferences. It then went on to specify the levels of treatment which could be indicated in the order regarding life sustaining treatment.[3] The controversy that provision created from its characterization by former governor Sarah Palin as "death

panels" scuttled its adoption. Governor Palin's actions may well have also prevented a fuller discussion of the cultural issues which have evolved over the past forty-six years about the role of death as part of life and its place in the health care continuum. This session will bring that discussion to the fore in the hope that a more dispassionate and analytical debate can occur within our society to begin to bring about a change in our death-denying culture.

I. Patient Self Determination Act

The Patient Self Determination Act (PSDA) took effect in 1991. Its goal was to alert individuals to their right under state law to have an advance directive to designate what health care they preferred, especially at the end of life, and also to inform them of the right to have some type of health care surrogate to assist them in making decisions if and when their condition did not permit them to do so. The PSDA grew out of the situation involving Nancy Cruzan. Its principal sponsor in the Congress, Missouri Senator John C. Danforth, was well aware of the circumstances surrounding the Cruzan case. Senator Danforth hoped that it would offer the least intrusive method by which to encourage individuals receiving services paid for by government third-party payors to engage in some type of health and end of life planning. Senator Danforth also hoped that it would avoid a repeat of the Cruzan situation and encourage people to take personal responsibility for making choices both in terms of what type of care they did or did not want and to appoint the person who could act as their health care surrogate in the event they were unable to make those decisions. As Dee Leahman points out in his article "Why the Patient Self-Determination Act Has Failed,"[4] only 30% of Americans have advance directives. In addition, while patients and their families prefer to die at home, four of five deaths in the United States take place in hospitals and nursing homes. Leahman points out that the emphasis in the PSDA is on documents rather than conversation. Since no one likes to talk about death, those conversations rarely occur. This in spite of the fact that some studies have shown that patients do want honest answers from their physicians, with 88% wanting to understand treatment options, and 74% fearing to die painfully, but only 11% of patients had spoken to their physicians about their concerns.[5]

Studies that were done several years after the enactment of the PSDA found that: "many clinicians consider a 'good patient' to be one who does what they suggest with a minimum of interference. Patients who want to take a more active role in their own treatment can take more time than passive patients. They may want better explanations of what treatments have been ordered for them and why. In spite of the extra time needed to answer questions, benefits accrue to the organization from treating adult patients, and parents of sick or injured children, like the adults they are."[6] Dr. Summers' article quoted from a study in 1980s published by the President's Commission for the Study of Bioethical Problems in Medicine which found that:

(1) patients who were more involved in the decision-making about their treatment had a more rapid recovery;

(2) these patients reported less pain and needed less pain medication;

(3) these patients were no more likely to report having any of the side effects or complications described to them about their treatment, but they were more likely to identify their side effects or complications as one of those described; and

(4) these patients were less likely to file a malpractice claim if the negative side effects or complications took place."[7]

II. Medicare

This paper need not dwell on the goal of the Medicare program. That subject has been ably dealt with for the forty-six years in which it has existed. However, one consequence of the infusion of hundreds of millions of dollars of capital into the health care system has been the development of sophisticated diagnostic and treatment technology together with advancements in durable medical equipment and the very concepts of what can be accomplished through the health care system. As a result, life expectancy has increased substantially, but more importantly, the expectations of Americans about their ability to survive what previously were fatal conditions or injuries has created a death-denying culture within the United States. All Americans know that they will die; they just simply do not believe they will do so very soon. Life can be extended by transplants of various organs, other replacements of bodily parts with artificial ones or the use of medications which provide seemingly miraculous cures. Those expectations have fueled a health care industry which is the envy of the world. However, it has also fueled a legal system which takes advantage of the expectations of the populous to recover large sums of money in malpractice litigation with claims of negligence based on outcomes which result either in death or increased morbidity but pled as unnecessary or avoidable. This has produced a medical-legal complex that itself has made it difficult for providers and patients to engage in frank and honest discussions about health care.

An article by Atul Gawande, MD, entitled "Letting Go: What Should Medicine Do When It Can't Save Your Life?" describes this situation well.[8]

The Physician Orders for Life-Sustaining Treatment is a medical order form which accomplishes two purposes. It turns treatment wishes of an individual into actionable medical orders, and it is portable as patients move from one care setting to another.

As Dr. Gawande points out, physicians are neither trained to engage in these discussions nor comfortable doing so. He found that patients appreciate this discussion and usually make the correct decisions as a result of the information provided.

The cost to society and patients in terms of both quality of life and dollars is illustrated in a number of articles. The Dartmouth Institute For Health Policy & Clinical Practice, as part of its "Atlas Project," recently published an article entitled "Trends and Variation in End-of-Life Care for Medicare Beneficiaries with Severe Chronic Illnesses."[9] The study supports the use of palliative and hospice care and the use by physicians of conversations with patients to determine the care that patients really want to receive. The report notes that: ". . . regions and hospitals with high-intensity patterns of care for patients with serious chronic illness have been found to have high hospital and specialist utilization rates in the first year after a heart attack; more aggressive care for patients with advance cancer who are near the end of life; and higher readmission and hospitalization rates for potentially avoidable causes of hospitalization."[10] The report notes elsewhere that the "greater amount of hospice care is accompanied by a decrease in the cost of end-of-life care."[11] The study explains that the variations found in the treatment of chronically ill Medicare patients may depend largely on the "systems of care within different regions and hospitals."[12]

III. The Patient Protection Affordability Care Act

When §§138 and 1233 of H.R. 3200, the earlier version of the Affordability Care Act, were proposed, the legislation had already been regarded as controversial for many reasons. Its highly prescriptive nature and the method by which it was being enacted created suspicion among many Americans that the real objective by the government as the largest single third-party payor in the country was only to save money rather than improve health care. Therefore, when the phrase "death panels" was used to describe the mechanisms and requirements contained in these two proposed sections, it merely reenforced for many Americans the fears that they harbored about the overall legislation. Whether this was a failure by the then-leadership in Congress or the political exploitation of a situation by opponents of the administration, the fact remains that those provisions failed to be enacted. Perhaps this failure echoed the choice made in 1990 in the PSDA to require only documentation and not conversation about advance directives and end of life care.

Medicare has also changed the prevalence of the conditions from which we die. During the last century, chronic diseases displaced infectious diseases and injury as the leading causes of death.[13] For example, in 1900 the number one cause of death was pneumonia. In 2000, it was heart disease. In 1900, the number two cause of death was tuberculosis. In 2000, it was cancer. While the age of death in 1900 was 47, in 2000, it was 75. In 1900, the place of death was a person's home. In 2000, it is more likely the hospital. Of course in 1900, medical expenses were covered by the family, whereas in 2000, most medical expenses were covered by Medicare. In 1900, there was not that much disability before death, whereas in 2000 the average disability before death was two years.[14]

The demographics are well known. The number of people over age 85 will double to ten million by the year 2030. Twenty-three percent of Medicare patients with over four chronic conditions account for 68% of all Medicare spending. Ten percent of Medicare beneficiaries have over five chronic conditions and drive two-thirds of Medicare spending. Ninety-five percent of all health care spending is for the chronically ill.

IV. Culture Change

Studies done to determine what patients with serious illnesses want reveal that they desire to control pain and symptoms, to avoid inappropriate prolongation of the dying process, achieve some control over their end of life, to relieve the burdens on their family and to strengthen

relationships with loved ones.[15] However, data from some studies, indicate that fifty percent of patients with life-threatening illnesses die within six months of entry into a hospital and had moderate to severe pain in the last three days of life, and thirty-eight percent of those who died spent more than 10 days in an intensive care unit in a coma or on a ventilator.[16]

Recent studies show that family caregivers would like to have their loved ones' wishes honored, to be included in the decision making processes, to receive some type of support or assistance at home, including practical help with transportation, medicines, and equipment, to have help with the activities of daily living for their loved ones, such as bathing, feeding and toileting, honest information, continual access to professional caregivers, to be listened to, to have their privacy respected, and to be remembered and contacted after the death of a loved one. Other studies show that family members do not believe they have enough contact with the physicians, enough emotional support, enough information about what to expect with the dying process, and enough help with pain.[17]

When the marketplace factors are considered, it should be noted that most health care systems pay providers for procedures, chemotherapy, clinical visits, and emergency room visits as opposed to caregiving, communication, pain control, home visits, or 24- hour on-call nursing. While hospice and other palliative care programs have grown dramatically in the past decade, payment limitations make full integration of these programs more difficult. For example, a person entering Medicare hospice relinquishes the right to have Medicare pay for direct care. In fact, this is merely a continuation of the segregation Medicare has instituted for different types of care modalities, providers, and care settings. Further exacerbating the situation is the relative lack of enforcement of quality standards.

Studies have shown that palliative care patients have a higher quality of life, and lower depression rates at twelve weeks after diagnosis, use less aggressive care, use more hospice care, and live longer after diagnosis.[18] Studies have also shown that palliative care clarifies goals of care with patients and families, helps families to select medical treatment and care settings to meet their goals, and assists with decisions to leave the hospital or to withhold or withdraw death-prolonging treatments that do not help to meet their goals.[19]

The provisions of the Accountable Care Act are being implemented through pilot projects and other initiatives to provide an opportunity to create a cultural change by encouraging providers to achieve certain economic goals. One is the Bundling Pilot Project whereby the government will test whether placing payments within a single provider who then pays for services and items needed for an episode of care will create shared savings. Another is the concept of the Accountable Care Organization ("ACO"). The ACO is supposed to encourage greater collaboration and cooperation among providers to achieve cost savings which can be shared between them. This concept would achieve cost savings by adding palliative care and hospice to the mix of alternative services to be considered for patients. Cost savings can also be achieved for the "medical home," the concept in the Accountable Care Act to provide comprehensive care that facilitates partnerships between individual patients and their personal providers and, when appropriate, the patient's family. Since payment to physicians coordinating care in the medical home is on a per member per month basis, the cost savings that can be achieved by palliative care and hospice could be significant. Other demonstration projects such as the "Independence and Home" demonstration project could benefit from palliative care and hospice. This concept will test which of the following provisions will achieve cost savings: the provision of physician or nurse practitioner-directed home-based primary care and care coordination across all treatment settings for beneficiaries with two or more chronic conditions, a non-elective hospital admission in the last year, prior rehabilitation or two or more functional dependencies.

Under the Accountable Care Act there will be quality reporting requirements for hospices beginning in 2014. It is presumed that accrediting standards will develop to meet that requirement.

As the debate continues between those who favor single payor universal coverage and those who wish to maintain a system which engenders personal responsibility in individuals seeking care, consideration must be given to the structure of existing health care delivery systems to determine whether they are shaping the choices of the patients and their families.

Of course, the cost for health care does not just fall on the government but falls on employers because of our system of workplace health care benefits. Fairly recent studies have shown that the estimated lost productivity of working caregivers to be $17.1 billion to $33.6 billion per year in 2002/2003. Two point four percent of caregiving employees left the workforce entirely in 2004.[20] These numbers may not capture the entire cost to the employer. The cost of lost productivity when employees are distracted by health care decisions can add to the numbers. While 67% of people state that they prefer to die at home, only 26% actually do so.[21] For employers offering health benefits, the direct cost is substantial with 25% of expenses being paid during the last year of a person's life.[22] If employers would support the development of programs to encourage conversations about

A good death is one which is "free from avoidable distress and suffering for patients, families, and caregivers in accordance with patients' and families' wishes and consistent with clinical, cultural, and ethical standards."

end of life issues, the completion of advance directives, and help in identifying health care proxies, it could result in substantial cost savings to them while at the same time allowing the private sector to effect a culture change without direct government involvement.

There are other public policy implications. Studies have shown that there is a substantial difference in the level of care at the end of life based upon a person's race. African Americans were almost twice as likely as caucasians and others to choose full code status and half as likely to choose withdrawal of life support.[23] Other studies have shown that black patients tend to receive less information from physicians than white patients do; and family members of black patients who have died describe more communication problems at the end of life than families of white decedents.[24] The same study showed that hospice care is under-used among black patients at the end of life.[25]

Studies of the effects of palliative or hospice care on Medicaid expenditures show a similar cost savings.[26] For example, patients who are provided with palliative care and died in the hospital had lower intensive care costs by almost 50%.[27] There is an approximately 25% decrease in costs for patients discharged alive from the hospital.[28] These cost savings can be significant since studies show that approximately 60% of all Medicaid spending is spent on acute hospital services and that the sickest 5% of patients with Medicaid coverage, largely the elderly and disabled, account for fully 50% of total program spending.[29] The dually eligible nursing home population represents 7% of the Medicaid population but accounts for 52% of Medicaid spending. Therefore, these cost savings from palliative care and hospice should be considerable among this population as well.[30]

The government's regulatory policies themselves can maintain and even reinforce the death-denying culture of our society. Even for end-of-life care, when provided in a nursing home - a common site for such care - the current quality measures are based on the minimum data set, which focuses on restoration and maintenance of functioning and do not include indicators appropriate to end-of-life care.[31] The quality measures in nursing homes, such as functional decline, weight loss, reduced respiration, and dehydration are frequently cited as deficiencies, but they are part of the end-of-life process. The minimum data set measures are used in regulatory oversight and public reporting thus encouraging more care at the end of life in that setting than may be needed or appropriate.[32]

Laws and practice are gradually beginning to accommodate the wishes of patients in more practical ways. The Physician Orders for Life-Sustaining Treatment (POLST) is a medical order form which accomplishes two purposes. It turns treatment wishes of an individual into actionable medical orders, and it is portable as patients move from one care setting to another. It honors the patient's end-of-life treatment preferences whether they are to limit treatment or to continue normal care. It does not replace the advance directive. While the advance directive is needed to appoint a health care surrogate and provide instructions for future life-sustaining treatments, the POLST accompanies an advance directive as a physician order.

There are needed changes in the Medicare requirements for hospice care. The current six-month terminal prognosis is a barrier for persons with non-cancer chronic terminal illnesses. That is because it is difficult to predict the death of these patients. This requirement affects persons dying in skilled nursing facilities and other settings. However, 72% of persons with non-dementia chronic terminal illnesses do not die in skilled nursing facility settings. Another requirement is that persons entering hospice must forego other Medicare Part A care when such care is related to the terminal illness. This results in hospital care and curative treatments being abandoned. The elimination of this prohibition would better account for the needed change in the intensity of hospice services toward the end of life.

Perhaps society is ready to put into practice the "good death" concept coined by the Institute of Medicine report from the late 1990s. A good death is one which is "free from avoidable distress and suffering for patients, families,

and caregivers in accordance with patients' and families' wishes and consistent with clinical, cultural, and ethical standards."[33] On the other hand, a "bad death" is one that "includes needless suffering, disregard for patient or family wishes or values, and a sense among participants that norms of decency have been offended."[34]

V. Legal and Ethical Issues

The case of Cruzan v. Director, Missouri Department of Health[35] contains the following statement by Chief Justice Rehnquist writing for the majority:

The principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred by our prior decisions . . . .[36]

In doing so, Chief Justice Rehnquist avoided explicitly recognizing a liberty interest in the freedom from unwanted medical intervention within the Fourteenth Amendment to the United States Constitution. On the other hand, physicians have argued that they have an ethical duty to discontinue treatment when professionally they believe it no longer meets the standard of care. There appears to be no clear legal precedent on the subject of whether a patient has the right to receive treatment he or she demands. In the absence of judicial sanction, a physician who chooses on professional and ethical grounds to discontinue treatment demanded by a patient may suffer liability.[37]

Attorneys today and certainly in the future will be facing questions from their provider clients about the legal and ethical obligations related to end-of-life care. As the government becomes more involved in the creation of standards of practice, it is not unforeseen that physicians will have a professional obligation under these new standards of care to advise their patients about non-treatment options as part of the health care delivery process, and providers will want advice on the risks involved in doing so. Is one of those risks the failure to advise patients fully of the consequences of non-treatment? In those situations will death be considered to be "wrongful"? What role will "informed consent" play when patients are advised of non-treatment options? How far will physicians have to go in explaining the consequences of a patient electing to forego treatment? Will decisions by hospital ethics committees sufficiently shield a physician from liability when the choice is made to deny care in the form of organ transplants or, conversely, for faith-based hospitals refusal to discontinue futile care?

Attorneys are well advised to begin to give thought to these questions and to consider developing within their firm expertise to answer them.

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Getting Comfortable With Near-Death Experiences

Dutch Prospective Research on Near-Death Experiences During Cardiac Arrest

by Pim van Lommel, MD

One cannot avoid the conclusion that endless or nonlocal consciousness has always existed and will always exist independently from the body, because there is no beginning nor will there ever be an end to our consciousness.



Pim van Lommel, MD, worked from 1977-2003 as a cardiologist in Hospital Rijnstate, a teaching hospital in Arnhem, the Netherlands, and is now doing full-time research on the mind-brain relation. Through his research on near-death experiences in survivors of cardiac arrest, he is the author of over 30 articles, one book, and several chapters about NDE.
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Abstract

In Dutch prospective studies on near-death experiences (NDE) in survivors of cardiac arrest, 18% of the 344 included patients reported such an experience of enhanced consciousness during the period of unconsciousness, during clinical death, during a transient functional loss of the cortex and the brainstem. An NDE seems to be an authentic experience which cannot be simply reduced to oxygen deficiency, imagination, fear of death, hallucination, psychosis, or the use of drugs, and people appear to be permanently changed by an NDE during a cardiac arrest of only several minutes duration.

Introduction

A near-death experience (NDE) can be defined as the reported memory of a range of impressions during a special state of consciousness, including a number of unique elements such as an out-of-body experience, pleasant feelings, seeing a tunnel, a light, deceased relatives or a life review, and a conscious return into the body. Many circumstances are described during which NDEs are reported such as cardiac arrest (clinical death), shock after loss of blood (childbirth), coma caused by traumatic brain injury or stroke, near-drowning (children) or asphyxia; also in serious diseases not immediately life-threatening, during isolation, depression or meditation, or without any obvious reason. Similar experiences to near-death ones can occur during the terminal phase of illness and are called "deathbed visions" or "end-of-life experiences."

So-called "fear-death" experiences are mainly reported after situations in which death seemed unavoidable like serious traffic or mountaineering accidents and "shared-death" experiences are reported by bystanders at the moment of death of a close relative. The NDE is usually transformational, causing enhanced intuitive sensitivity, profound changes of life-insight and the loss of fear of

death. The content of an NDE and the effects on patients seem similar worldwide, across all cultures and all times. However, the subjective nature and absence of a frame of reference for this ineffable experience lead to individual, cultural, and religious factors determining the vocabulary used to describe and interpret this experience.[1] Near-death experiences occur with increasing frequency because of improved survival rates resulting from modern techniques of resuscitation and from new therapies for patients with cerebral trauma. According to a recent random poll in the U.S. and in Germany, about four percent of the total population in the western world have experienced an NDE. [2,3] Thus, about nine million people in the U.S., about two million people in the United Kingdom and about 20 million people in Europe should have had this extraordinary conscious experience. A NDE seems to be a relatively regularly occurring, and, to many physicians, an inexplicable phenomenon and hence an often ignored result of survival in a critical medical situation. After all, according to current medical knowledge it is impossible to experience consciousness during cardiac arrest or deep coma.

Until quite recently there was no prospective and scientifically designed study to explain the cause and content of an NDE, all studies had been retrospective and very selective with respect to patients. Based on these incomplete retrospective studies, some believed the experience could be caused by physiological changes in the brain as a result of lack of oxygen (cerebral anoxia), other theories encompass a psychological reaction to approaching death, hallucinations, dreams, side effect of drugs, or just false memories. So properly designed prospective studies in survivors of cardiac arrest are necessary in order to obtain more reliable data to corroborate or refute the existing theories on the cause and content of a NDE. We needed to know if there could be a physiological, pharmacological, psychological or demographic explanation why people experience enhanced consciousness during a period of cardiac arrest.

The Dutch Prospective Study on NDE in Survivors of Cardiac Arrest

In 1988 a prospective study was initiated in the Netherlands.[4] At that point, no large-scale prospective study into NDEs had been undertaken anywhere in the world. Our study aimed to include all consecutive patients who had survived a cardiac arrest in one of the ten participating Dutch hospitals. This prospective study would only be carried out among patients with a proven life-threatening crisis. All of these patients would have died of cardiac arrest had they not been resuscitated within five to ten minutes. This kind of design also creates a control group of patients who have survived a cardiac arrest but who have no recollection of the period of unconsciousness. In a prospective study such patients are asked, within a few days of their resuscitation, whether they have any recollection of the period of their cardiac arrest, i.e., of the period of their unconsciousness. All patients' medical and other data are carefully recorded before, during and after their resuscitation. We always collected a record of the electrocardiogram during the cardiac arrest of all patients included in our study. The advantage of this prospective study design was that all procedures were defined in advance and no selection bias could occur. Within four years, between 1988 and 1992, 344 successive patients who had undergone a total of 509 successful resuscitations were included in the study. All the patients in our study had been clinically dead and in the first stage of the process of dying. The Dutch study was published[4] in the *Lancet* in December 2001.

Results of the Dutch Prospective Study

If patients reported memories from the period of unconsciousness, the experiences were scored according to a certain index, the WCEI, or "weighted core experience index."[5] The higher the number of elements reported, the higher the score and the deeper the NDE. We found that 282 patients (82%) had no recollection of the period of their unconsciousness, whereas 62 patients - 18% of the 344 patients - reported a NDE. Of these 62 patients with memories, 21 patients (6%) had some recollection; having experienced only some elements, they had a superficial NDE with a low score. Because of the prospective design of the study, we also included these patients. And 42 patients (12%) reported a core experience: 18 patients had a moderately deep NDE, 17 patients reported a deep NDE and six patients a very deep NDE. The following elements were reported: half of the patients with a NDE were aware of being dead and had positive emotions, 30% had a tunnel experience, observed a celestial landscape or met with deceased persons, approximately one-quarter had an out-of-body experience, communication with 'the light' or perception of colors, 13% had a life review and 8% experienced the presence of a border. All the familiar elements of a

We were particularly surprised to find no medical explanation for the occurrence of a Near Death Experience, because all the patients in our study had been clinically dead.

NDE were reported in our study, with the exception of a frightening or negative NDE.

Were there any reasons why some people, but most people do not, recollect the period of their unconsciousness?

In order to answer this question, we compared the recorded data of the 62 patients with a NDE to the data of the 282 patients without NDE. To our surprise we did not identify any significant differences in the duration of the cardiac arrest (2 minutes or 8 minutes), nor differences in the duration of unconsciousness (5 minutes to three weeks in coma). So we failed to identify any differences between the patients with a very long or a very brief cardiac arrest. It was established that medication played no role. A psychological cause such as the infrequently noted fear of death immediate before the arrest did not affect the occurrence of a NDE. Whether or not patients had heard or read anything about NDE in the past also made no difference. Any kind of religious belief, or indeed its absence in non-religious people or atheists, was irrelevant and the same was true for the level of education. Only the large-scale Dutch study allowed for statistical analysis of the factors that may determine whether or not an NDE occurs.

As a result of our study, we could exclude physiological, psychological, pharmacological and demographic explanations for the occurrence of a NDE. We were particularly surprised to find no medical explanation for the occurrence of a NDE, because all the patients in our study had been clinically dead. Only a small percentage reported an enhanced consciousness with lucid thoughts, emotions, memories, and sometimes perception from a position outside and above their lifeless body while doctors and nursing staff were carrying out resuscitation. And because of some cases of veridical perception during resuscitation we reached the inevitable conclusion that patients experienced all the aforementioned NDE elements during the period of their cardiac arrest, during the total cessation of blood supply to the brain. Nevertheless, the question how this could be possible remained unanswered. See Figure 1.

Results of the Dutch Longitudinal Study

Our Dutch study was also the first to include a longitudinal component with interviews after two and eight years, using a standardised inventory featuring 34 life-change questions, which allowed us to compare the processes of transformation between people with and without NDE.[6] The question was whether the customary changes in attitude to life after a NDE were the result of surviving a cardiac arrest or whether these changes were caused by the experience of a NDE. This question had never been subject to scientific and systematic research with prospective design before. Among the 74 patients who consented to be interviewed after two years, 13 of the total of 34 factors listed in the questionnaire turned out to be significantly different for people with or without a NDE. The second interviews showed that in people with NDE in particular fear of death had significantly decreased while belief in an afterlife had significantly increased. We were surprised to find that the processes of transformation that had begun in people with NDE after two years had clearly intensified after eight years. We saw in them a greater interest in spirituality and questions about the purpose of life, as well as a greater acceptance of, and love for, oneself and others. The conversations also revealed that people had acquired enhanced intuitive feelings after a NDE, along with a strong sense of connectedness with others and with nature. Or, as many of them put it, they had acquired 'paranormal gifts.' The sudden occurrence of this enhanced intuition, or nonlocal perception, can be quite problematic, as people suddenly have a very acute sense of others, which can be extremely intimidating.

The integration and acceptance of a NDE is a process that may take many years because of its far-reaching impact on people's pre-NDE understanding of life and value system. Finally, it is quite remarkable to see a cardiac arrest lasting just a few minutes give rise to such a lifelong process of transformation. For obvious reasons most people feel nostalgic about their NDE because of the unforgettable feelings of peace, acceptance, and love they encountered during the experience, and the feeling of being forced to return back into the body. We identified a distinct pattern of change in people with a NDE and revealed that integrating these changes into daily life is a long and arduous process because there is at first hardly any acceptance by oneself as well as by others, like doctors, nurses, family members, partner and friends. This makes the process of coming to terms with the experience difficult and painful. So the NDE is often a traumatic event with many years of strong feelings of depression, homesickness and loneliness.[6]

Other Prospective Studies on NDE in Survivors of Cardiac Arrest

Bruce Greyson, who published a prospective study in 116 survivors of cardiac arrest in the USA[7], found that 15.5% of the patients reported a NDE: 9.5% reported a core NDE and 6% a superficial NDE. He writes that "no one physiological or psychological model by itself could explain all the common features of an NDE. The paradoxical occurrence of a heightened, lucid awareness, and logical thought processes during a period of impaired cerebral perfusion raises particular perplexing questions for our current understanding of consciousness and its relation to brain function. A clear sensorium and complex perceptual processes during a period of apparent clinical death challenge the concept that consciousness is localized exclusively in the brain."

Sam Parnia and Peter Fenwick from the UK included in their prospective study 63 patients who survived their cardiac arrest.[8] They found that 11% reported a NDE: 6.3% reported a core NDE, and 4.8% a superficial NDE. They report that the NDE cases with veridical perceptions during cardiopulmonary resuscitation (CPR) suggest that the NDE occurs during the period of unconsciousness. This is a surprising conclusion, in their view, because "when the brain is so dysfunctional that the patient is deeply comatose, those cerebral structures, which underpin subjective experience and memory, must be severely impaired. Complex experiences as reported in the NDE should not arise or be retained in memory. Such patients would be expected to have no subjective experience, as was the case in the vast majority of patients who survive cardiac arrest, since all centers in the brain that are responsible for generating conscious experiences have stopped functioning as a result of the lack of oxygen." Over a period of four years Penny Sartori carried out an even smaller prospective study into NDE in 39 survivors of cardiac arrest in the UK.[9] She found that 23% reported a NDE: 18% reported a core NDE, and 5% a superficial NDE. She concludes that "according to mainstream science, it is quite impossible to find a scientific explanation for the NDE as long as we 'believe' that consciousness is only a side effect of a functioning brain." The fact that people report lucid experiences in

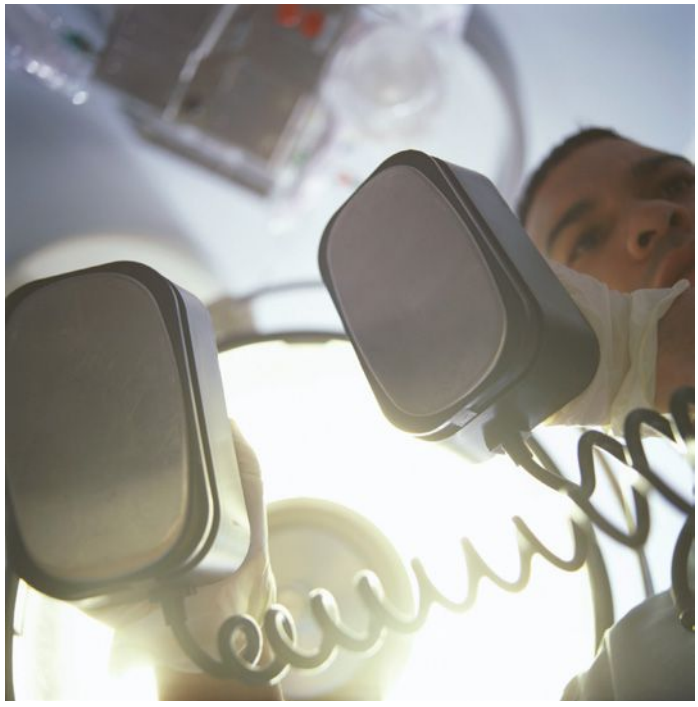


Figure 1
Only a small percentage of those clinically dead reported an enhanced consciousness with lucid thoughts, emotions, memories, and sometimes perception from a position outside and above their lifeless body while doctors and nursing staff were carrying out resuscitation.

their consciousness when brain activity has ceased is, in her view, "difficult to reconcile with current medical opinion."

Summary Scientific Research on Near-Death Experiences

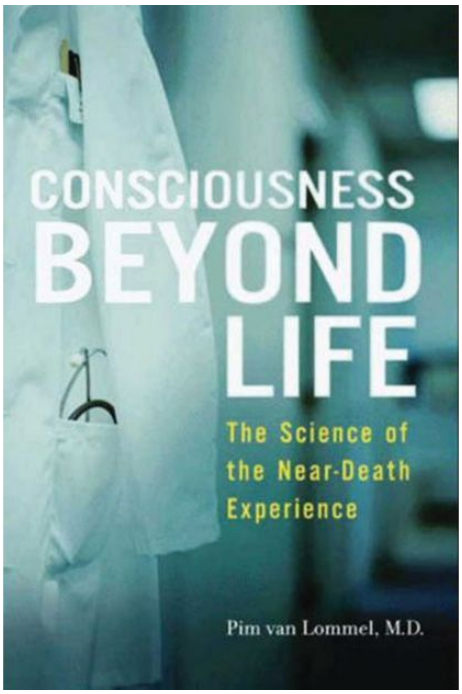
In four recently published prospective studies on NDE in survivors of cardiac arrest, with identical study design, between ten and twenty percent of a total of 562 included patients reported an experience of enhanced consciousness during the period of apparent unconsciousness, during clinical death. With our current medical and scientific concepts it seems impossible to explain all aspects of the subjective experiences as reported by patients with an NDE during a transient functional loss of the cortex and the brainstem. Scientific studies into the phenomenon of NDE highlight the limitations of our current medical and neurophysiological ideas about the various aspects of human consciousness and the relationship between consciousness and memories on the one hand and the brain on the other. The prevailing paradigm holds that memories and consciousness are produced by large groups of neurons or neural networks. For want of evidence for the aforementioned explanations for the cause and content of a NDE the commonly accepted, but never proven, assumption that consciousness is localised in the brain should be questioned. After all, how can an extremely lucid consciousness be experienced outside the body at a time when the brain has a transient loss of all functions during a period of clinical death, even with a flat EEG?[10] Furthermore, even blind people have described veridical perceptions during out-of-body experiences at the time of their NDE. [11]

Nonlocal Consciousness

It is a scientific challenge to discuss new hypotheses that could explain: the reported interconnectedness with the consciousness of other persons and of deceased relatives; to explain the possibility of experiencing instantaneously and simultaneously (nonlocality) a review and a preview of someone's life in a dimension without our conventional body-linked concept of time and space, where all past, present and future events exist and are available, and the possibility to have clear and enhanced consciousness with persistent and unaltered 'Self'-identity, with memories, with cognition, with emotion, with the possibility of perception out and above the lifeless body, and even with the experience of the conscious return into the body. In my recent book[12] I describe a concept in which our endless consciousness with declarative memories finds its origin in, and is stored in a nonlocal realm as wave-fields of information, and the brain only serves as a relay station for parts of these wave-fields of consciousness to be received into or as our waking consciousness. The latter relates to our physical body. These informational fields of our nonlocal consciousness become available as our waking consciousness only through our functioning brain in the shape of measurable and changing electromagnetic fields. The function of the brain should thus be compared with a transceiver, a transmitter/receiver, or interface, exactly like the function of a computer. Different neuronal networks function as interface for different aspects of our consciousness, and the function of neuronal networks should be regarded as receivers and conveyors, not as retainers of consciousness and memories.

In this concept, consciousness is not rooted in the measurable domain of physics, our manifest world. This also means that the wave aspect of our indestructible consciousness in the nonlocal realm is inherently not measurable by physical means. However, the physical aspect of consciousness can be measured by means of neuroimaging techniques like EEG, fMRI, and PET-scan. There is a kind of biological basis of our waking consciousness, because during life our physical body functions as an interface or place of resonance. But there is no biological basis of our whole, endless, or enhanced consciousness because it is rooted in a nonlocal realm. Our nonlocal consciousness resides not in our brain and is not limited to our brain, and our brain seems to have a facilitating, and not a producing function to experience consciousness. One cannot avoid the conclusion that endless or nonlocal consciousness has always existed and will always exist independently from the body, because there is no beginning nor will there ever be an end to our consciousness. For this reason we should seriously consider the possibility that death, like birth, can only be a transition to another state of consciousness. According to this idea death is only the end of our physical aspects, and during life our body functions as an interface or place of resonance for our nonlocal consciousness.

This view of a nonlocal consciousness also allows us to understand a wide variety of special states of consciousness,[13] not only near-death experiences, but also mystical and religious experiences, deathbed visions (end-of-life experiences), shared death experiences, peri-mortem and post-mortem experiences (after death communication, or nonlocal interconnectedness with the consciousness of deceased relatives), heightened intuitive feelings and prognostic dreams (nonlocal information



Consciousness Beyond Life

BOOK REVIEW

The Science of the Near-Death Experience

by Pim van Lommel, MD

Van Lommel provides scientific evidence that the near-death phenomenon is an authentic experience that cannot be attributed to imagination, psychosis, or oxygen deprivation. He further reveals that after such a profound experience, most patients' personalities undergo a permanent change. In van Lommel's opinion, the current views on the relationship between the brain and consciousness held by most physicians, philosophers, and psychologists are too narrow for a proper understanding of the phenomenon. In Consciousness Beyond Life, van Lommel shows that our consciousness does not always coincide with brain functions and that, remarkably and significantly, consciousness can even be experienced separate from the body.

Source: Amazon.com / Paperback: 448 pages Publisher: HarperOne; Reprint edition (August 9, 2011) / ISBN-10: 0061777269 / ISBN-13: 978-0061777264

exchange), remote viewing (nonlocal perception) and perhaps even the effect of consciousness on matter like in placebo-effect or neuroplasticity,[14,15] where in EEG, fMRI and PET-scan studies functional and structural changes in the brain are demonstrated following changes in consciousness (nonlocal perturbation).

Conclusion

It often takes an NDE to get people to think about the possibility of experiencing consciousness independently of the body and to realize that presumably consciousness always has been and always will be, that everything and everybody is connected in higher levels of our consciousness, that all of our thoughts will exist forever, and that death as such does not exist. Only if we are willing and able to ask open questions and abandon preconceptions research into NDE may help the scientific community to reconsider some unproven assumptions, not only about life and death, but above all about consciousness and its relation with brain function.

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MM

Medicine & "Connections"

by James B. Wolfe, MD

A possible solution is legislation that would allow the unmatched medical students to serve as physician extenders of rural primary care physicians.



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The TV series "Connections" is probably quite familiar to readers born prior to 1960. For those who are unfamiliar with the series let me just say that James Burke, the author of the series, wove a complex web of interconnected events over many centuries resulting in our modern day technologies.

Today, I would like to delve into the web that has created our present post-graduate medical education system in the U.S.

Although American physician education goes much further back than 1900, I would like to use that date as my starting point. Evidently, medical education provided by the 155 medical schools was quite poor at that time. In 1910, the Carnegie Foundation asked Abraham Flexner, an educator, to review the quality of the U.S. and Canadian medical schools. As a result of his extensive report after visiting the schools, all but five of the schools were declared deficient and many were forced to close. Flexner identified Johns Hopkins University School of Medicine, where Dr. William Osler created the first residency program, as the model for medical schools. This model had a clinical setting where new physicians could gain experience treating patients, high quality teaching, and a research program. Over the ensuing decades this model spread across our country.

However, outside the regional teaching centers, medical treatment advanced slowly until after World War II. This conflagration had the beneficial effect of rapidly advancing medicine with the introduction of penicillin, advancement in surgical procedures, and the creation of rehabilitation programs even in the "hinterlands." Thanks to the GI bill, a massive increase in physicians entering residencies occurred. The bill provided a generous living allowance to the physicians, and also provided a subsidy to the hospitals offering residency positions to servicemen. Improved outcomes resulted in patients increasing their respect for the community physicians at a time when 75% of the population had some kind of health insurance.

Competition among WWII wartime employers for employees was somewhat curtailed by wartime wage freezes. This led directly to employer-provided health insurance for the masses when the War Labor Board ruled that fringe benefits did not count as wages. As early as 1945 President Truman called for universal health insurance. Medicare was created in 1965 as a direct consequence of insurance rate profiling by insurance companies. Prior to 1965 less than 50% of elderly Americans had health insurance because their premiums were usually three times greater than their children. At the time of Medicare creation, Congress acknowledged the need to support medical education.

Medicare Part A paid the hospitals on a "cost of service" basis which included GME (graduate medical education) costs. Because private insurance reimbursements to hospitals were based on a "cost basis" that included GME expenses as well as capital expenditures, it should be no surprise that America saw runaway medical care inflation.

Fast forward to 1997; in an effort to deal with the runaway medical inflation Congress passed the Balanced Budget Act of 1997 (BBA97). In the years preceding the Act, various estimates were made that the U.S.A. would experience a surplus supply of physicians. Hence, there was not great opposition to restricting Medicare funding for residency training.

As a direct result of the advances in medical care the average life expectancy in America has increased over the last four decades. The post WWII baby boom and the Affordable Care Act of 2010 have added to the impending pressure on our health care system. To deal with the physician shortfall that is now forecast three groups have entered the scene:

1. Medical educators have either increased their medical school enrollment slots or started new medical schools within and outside of the continental U.S.
2. Advanced practice nurses are pushing for independent practice privileges throughout the U.S. asserting that they can replace family practitioners and some specialty activities.
3. Foreign-trained physicians are increasingly coming to the U.S. for residency training.

That brings us to today. Presently, there are more medical school graduates than there are residency slots. Last year, about 500 U.S.-trained medical students failed to match with a residency of their choice. Locally, three Missouri University medical students failed to match according to the Office of the Dean. If you consider that MU alone plans to add 30 medical students by 2016 and if you take into account the effect of compounding (each year the unmatched students will be joined by the new graduates), the numbers can become large fairly quickly.

At our January MSMA Council meeting, this problem was discussed. Edmond Cabbabe, MD, suggested that MSMA consider trying to offer legislation that would allow the unmatched medical students to serve as physician extenders of rural primary care physicians. This solution has several benefits:

- The unmatched students continue their medical education while waiting to match with a residency program.



James Burke is a British broadcaster, science historian, author, and television producer, who is known, among other things, for his documentary television series Connections (1978), and for its more philosophically oriented companion series, The Day the Universe Changed (1985), which is about the history of science and technology. The Washington Post called him "one of the most intriguing minds in the Western world". *Source & Photo: Wikipedia*

- The unmatched students would be able to start repaying their student loans since their compensation would be in line with physician assistants and/or APNs.
- Since MSMA envisions the program being open to unmatched students from any region of the U.S., it would allow future physicians to experience the many benefits of Missouri. Hopefully, some would return to practice in Missouri after successfully completing their residency.
- Under served rural patients would benefit from the program.
- It would lessen the APNs' argument for independent practice since they continually say that this would ensure migration of APNs to rural areas. (Do they think that we and the legislators have not studied the demographic facts?)
- The program would be revenue neutral or even positive (license fees) to the state.

Rep. Keith Fredrick, DO, filed the above legislative language in the Missouri House (HB 1842) in February and had its Committee hearing on February 26th. MSMA will lobby hard for the passage of this legislation. I would hope that all Missouri physicians would join with us by asking their state legislators to support this bill. This type of "out of the box" forward thinking and the programs beneficial to young physicians implemented this year is why I feel that all Missouri physicians should be members of MSMA.

Since this is my last President's Forum article I would like to thank all MSMA members for the privilege of serving as your servant and spokesman for the last year. **MM**

Congratulations *Missouri Medicine*

To the Editor: it gave me great pride to see *Missouri Medicine* quoted several times in this mornings *Wall Street Journal* (3/26/1014)article on the medical issues of running marathons. Your energetic and enlightened leadership continues to provide us with a journal with few rivals in quality, excellence, and practical usefulness. Your work has enlarged us all. Best regards.

Donald Sessions, MD
Missouri Medicine Editor 1988-1992
MSMA member since 1977
St. Louis, Missouri

Physician Fees Feel the Pressure

A recent article in the *Wall Street Journal* describing reductions of physician fees under the new health care plans gave the example of Blue Shield of California asking doctors to accept fees up to 30% lower than usual commercial rates. This is but one example of the continuing pressure on physician fees; implementation of the Affordable Care Act is virtually certain to exacerbate this trend.

My impression is that most people do not fully realize the implications of fee cuts on physician income. While some will have an empathetic response, many will believe that decreasing the income of those in the higher income brackets is just deserts, and may even engender a sense of *schadenfreude.* This emotion may be due in part to the implication that there is a permanently fixed income pie to divide, and that if one person earns less then another person therefore will earn more. This construct has recently become widely promulgated by the current administration.

Many people, including our patients, may assume that a 30% decrease in reimbursement is equivalent to a 30% decrease in physician income. However, it requires another step, a simple and fairly obvious calculation, to fully understand the practical effects of decreasing physician reimbursement. This critical additional step is rarely if ever mentioned in media reports concerning this topic.

The average overhead of a doctor's office is commonly estimated to be around 60%. If a physician's customary reimbursement for a service is, for example, $10, and allowing for an office overhead of 60% ($6), the doctor takes home $4.

Implementing a 30% decrease in payment for the $10 service, causes reimbursement to become $7. However, the overhead costs of this same patient encounter (employee salaries, office expenses, and other costs of medical practice) remain approximately the same at $6. Therefore, the physician takes home $1 instead of the former $4, an effective decrease of take-home of 75%.

The above basic calculation illustrates how a relatively small fee reduction has a leveraged effect on take-home pay. The extra step of analysis which incorporates overhead costs is essential to understand the net effect.

Significant physician fee cuts would have a major effect on the provision and availability of medical care. Regardless of the field of endeavor, not many people would be willing or able to continue in their same occupations if their income decreased by three-fourths.

Increased standardization, control, and concentration of medical care is accepted to be a goal of central health planners. The implementation of large integrated groups of medical practitioners facilitates oversight of both the provision of medical care and the providers of services.

The *Kansas City Star* recently published a series of reports on the business of medicine in Kansas City. It was reported that in the past decade Medicare fees have increased by 9% while overhead has increased by 27%.

Overhead inflation combined with lagging reimbursement threatens the viability of private medical practices. It should be made known that fee decreases will have the effect of dramatically altering the provision and availability of medical care.

Charles M. Lederer, MD
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"Doctor Fix" Only Helps Hospitals; Why Is the AMA Supporting It?

Endorsement of the misnamed "doctor fix" by physicians' organizations like the American Medical Association is troubling. It simultaneously erodes private practice finances while rewarding hospitals and the physicians they employ. Patients will suffer financially.

Deep within a recent 1,200 page Federal Register is a blatant case of price fixing by government fiat. The

"doctor fix" that the AMA is supporting gives physicians a 0.5% annual increase for coming years. The Senate recommendation has no increase. Hospitals are allowed to bill their employed physicians' services using 'outpatient' charges. An identical procedure or service billed by a hospital may cost 15% more than Medicare allows a private practitioner's office. Patient's deductibles are higher also. Hospitals will receive a 1.7% increase this year more than three times the proposed physician increase.

Physicians unable financially to remain open become hospital employees or leave medicine. This exacerbates the costs of medical care, invests the hospitals with potentially monopolistic control of U.S. health care and worsens the looming physician shortage.[1]

The AMA and other physician organizations should negotiate elimination of pecuniary limits on office services identical to those hospitals bill as outpatient services. The AMA should not endorse government policies which cost patients money and indenture private doctors to hospital systems.

The doctor fix is outrageously unfair to private practice physicians and unworthy of AMA support.

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Editor's Note:
Stolen Laptop Leads to $1,500,000 by Feds Against Teaching Hospital

In the January/February 2014 issue of *Missouri Medicine*, Contributing Editor Art Gale, MD, pointed out that rather than serving patients and physicians, electronic health records have enslaved both while failing to improve quality or reduce health care costs ("The Electronic Medical Records Fiasco"). Attorney Kimela West, JD warned of the astounding penalties associated with theft of computers with medical records, ("Patient Medical Information at Risk from Stolen Computers.")

I want to report an incident that occurred in 2012 that illustrates the uncompromising vindictiveness and unreasonableness of the bureaucracy that is the US Department of Health and Human Services (HHS). A physician on the faculty of Harvard Medical School and the Massachusetts Eye & Ear Hospital was in Korea to present a lecture. His laptop that contained about 3,500 unencrypted patients' records was stolen from his room. The incident was self-reported by the physician to HHS. There was no evidence that any medical information was compromised or any patient harmed.

HHS fined Massachusetts Eye & Ear Hospital $1,500,000 for this isolated incident with no patient harm. Undoubtedly the Feds would have made the fine larger but this was statutorily the maximum allowed by law.

Physicians are caught in an over-whelming avalanche of rules, regulations, mandates, laws, statues, mandatory guidelines that come from the ever-growing, ever-controlling, frequently vindictive, rarely effective Federal government. Physicians are being driven into early retirement, hospital/agency employment; some will go bankrupt. Compliance steals time from direct patient care and physician/patient interaction. Do you spend more time looking/talking/interacting with your patient? Or trying to create an audit proof electronic record?

Secure your patient electronic health records on server computers, laptops, and all electronic devices.

John C. Hagan III, MD
Editor, Missouri Medicine

Errata

Figure 1, page 97, in the Editorial Overview in this issue by Drs. McCullough and Lavie should have been correctly sourced to La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structured remodeling in endurance athletes. Eur Heart J 2012;33:998-1006. Figure 1 was sourced when it appeared as Figure 3, page 314 in *Missouri Medicine*, July/August 2012 to: Patil HR, O'Keefe JH, Lavie CJ, Magalski A, Vogel RA & McCullough PA. Cardiovascular damage resulting from chronic excessive endurance exercise. MO MED 2012;109:312-321. In personal communication with Andre La Gerche, MD, he indicates the original figure appeared in Sharma S, Zaidi A. Exercise-induced arrhythmogenic right ventricular cardiomyopathy: Fact or fallacy? European Heart Journal. 2012;33:938-940. Drs. McCullough, Lavie and *Missouri Medicine* and its Editor regret using the tertiary attribution rather than the original. **MM**

Missouri Medicine wishes to thank these non-Editorial Board physicians for peer-review in 2013: Lenard Politte, MD, William V. Stoecker MD, Jim Blaine, MD, Douglas Bogart, MD,Dragan Svrakic MD, and the coordinators of our four theme issues: John C. Morris, MD, Craig L. Franklin, DVM, PhD, Enrico Di Cera, MD, and Nicole M. Fearing, MD. Also thanks to Evelyn Vail, medical librarian, North Kansas City Hospital and Rebecca J. Hagan.

High Impact Journal *Circulation* Cites *Missouri Medicine* Paper

Authors take note. The February 2014 issue of *Circulation* featured a highlighted authoritative review article "New Frontiers in Endurance Exercise Biology: Running Forward" by Rowe, Safdar and Arany of the Harvard Medical School. Their reference 110 was: Patil HR, O'Keefe JH, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Cardiovascular damage resulting from chronic excessive endurance exercise. Mo Med. 2012;109:312–321. Kudos to the authors.

No other state medical journal article was cited including the *New England Journal of Medicine*. All Missouri Medicine content is linked with PubMed Central and EBSCOHost databases. Select *Missouri Medicine* content is posted to MedHelp.org a top world heath internet site with over 12 million unique visitors per month and their e-newsletter with over 300,000 subscribers. No other state medical journal except the NEJM can offer your papers and research such national and international exposure. For information on contributing to *Missouri Medicine* go to www.msma.org/MissouriMedicine and download from "Instructions for Authors/Style Sheet." The Journal is supported by the dues of current members of the Missouri State Medical Association. For membership information in MSMA contact Haley Wansing hwansing@msma.org.

Members in the News

Mark Adams, MD, MSMA member since 2009, Columbia, has been inducted into the 2014 Class of the Missouri Sports Hall of Fame in Springfield.

MSMA Second District Councilor **Sandra Ahlum, MD**, is chairing the C.H.A.R.T. Partnership this year and contributing, along with her husband and MSMA Past President **Lent Johnson, MD**, to a Teens Health Fair being held in Northeast Missouri on April 12.

Clara Applegate, MD, MSMA member since 2008, West Plains, spoke during the Women with Heart event in February about acute stroke signs, symptoms and intervention. Proceeds from the event went toward equipment and patients' needs for the Ozarks Medical Center stroke program and education.

A ribbon-cutting ceremony was held for the new Hannibal campus of Moberly Area Community College in early February, and Drs. **Christopher Bieniek** and **Curtis Barton**, MSMA members since 1992, of Midwest Orthopedic Specialists, were thanked for their land contributions of six acres upon which the facility was constructed.

Agape Clinic in Belle re-opened its doors in February thanks to the efforts of **Kathi Clement, MD**, MSMA member since 2003, Rolla, who stepped forward to provide her services in leading the practice.

MSMA member since 1977 and Chancellor Emeritus of Washington University **William H. Danforth, MD**, is one of the first recipients of the inaugural Excellence in Diversity and Inclusion Award presented during the third annual Celebration of Leadership Luncheon by the Vagabonds Foundation, Inc.

MSMA member since 2012, **Elizabeth Dang, MD**, was presented a proclamation by Jeff Davis, Mayor of the City of Belton, for Feb. 7 as National Wear Red Day in celebrating extraordinary progress in women's heart health.

The American Board of Family Medicine is pleased to announce the successful completion of its Certification Examination by **Janet Hankins, MD**, MSMA member since 1994, Clinton.

Congratulations to MSMA members and supporters of organized medicine for more than 50 years combined, Drs. **Joel Hassien** and **Priscilla Long**. Dr. Hassien accepted the "Support of Service" Award on behalf of Northeast Missouri Imaging Associates from the Hannibal Free Clinic for providing radiological interpretive services to patients at the free clinic. Dr. Long, who has volunteered there since 2007, received the "Caring Heart" Award.



Lovinger Doctors Serve as Physician(s) of the Day

A family of physicians from Nevada served as the Physicians of the Day at the Missouri Legislature in Jefferson City in February. The four of them, including Dr. **Warren Lovinger**, and three of his children, Drs. **Tom Lovinger, Sarah Florio,** and **Dan Lovinger,** a second-year UMC medical student, were introduced in the Missouri Senate and House of Representatives.



Missouri Society of Eye Physicians & Surgeons
Eye Screening Day at the Capitol

Vonda Cross with the Mason Eye Institute checks the vision health of Lieutenant Governor Peter Kinder.

Gary LaMonda, MD, MSMA member since 1980, conducted a meeting in Moberly in March to inform his patients of a new way in which he will be practicing medicine, referred to as MDVIP, designed to allow doctors to have smaller practices devoted to their client base.

Esteban Marten, MD, MSMA member since 2011, with Jefferson City Medical Group, was among 1,622 initiates from around the world to become Fellows of the American College of Surgeons during the recent convocation ceremony at the College's 2013 annual Clinical Congress in Washington, DC.

The Texas County Food Pantry Board recognized **Charles Mueller, MD**, MSMA member since 2000, Houston, for 12 years of service on their Board of Directors.

MSMA member since 1985, **Joseph Muscato, MD**, has been appointed Medical Director of the Stewart Cancer Center and, on Jan. 6, opened a new inpatient cancer treatment unit with 32 private patient rooms along with long-time cancer survivor Norm Stewart.

Joseph Parks, MD, MSMA member since 1993, had the honor of presenting two directors awards to Vicky Fairey during the Missouri Coalition of Community Mental Health Centers Annual Conference in St. Charles.

James Riscoe, MD, MSMA member since 1997, of Cedar County Memorial Hospital in El Dorado Springs was recently peer selected for 417 Magazine's list of "Top Doctors."

Capital Region Medical Center recently appointed to its leadership **Eston Schwartz, MD**, MSMA member since 2011, Jefferson City, as its chief of medicine.

Leo Shunyakov, MD, MSMA member since 2007, Bolivar, received an award as a "Leading Physician of the World" and "Top Oncology Specialist in Missouri" and will be included in the International Association of Healthcare Professionals' 2013 edition of The Leading Physicians of the World.

Anne Winkler, MD, MSMA member since 2003, Springfield, has been selected as one of 50 to participate in a nationwide RA assessment group called the Rheumatoid Arthritis Performance Project.

Rodney Yager, DO, and the staff of Hannibal Clinic in Monroe City donated more than 500 items to The Monroe City Food Bank under the name "Yager's Fruit Ninjas."

MM

AS I SEE IT

Bare Bones Medical Care

by Max Heeb, MD

The nurse said, "Not to worry. He comes at noon for emergencies."

We were sailing "bare boat" on a 47' x 25' catamaran sailboat from St. Lucia to Grenada. The crew included Captain Max, wife Marianna Heeb, Dr. Andrew McCanse, Dr. Barbara Buchanan McCanse, and two other couples.

Andy was past president of the Missouri State Medical Association, the Missouri State Surgical Society and an AMA Delegate. Barbara, a child psychiatrist, had been Speaker of the MSMA House of Delegates and had recently received the 2014 Life Time Achievement Award from Missouri University Medical School.

We were anchored off Petite St. Vincent, the last of a string of islands of the nation of St. Vincent. I was snorkeling near the boat enjoying the view of coral and beautiful fish in King Neptune's garden. Marianna screamed, "Max come quick! Andy needs you!"

I hurried to the swim ladder to find Andy in full pulmonary edema; he was cyanotic, coughing up rusty sputum; had a pleural effusion and rales up to the apices.

What to do? What to do? Should I call a May Day on the VHF? Time was of essence.

I pulled out my MASH UNIT, a sea bag with every thing from sea sick pills to suture kit and splints. Ah-ha! There was a bottle of Triemterine/HCTZ, in the cardiac zip lock bag.

I gave Andy a triple dose.

Fortunately our sister ship crew had hired a bona fide Captain. He knew of a hospital on Curacao, one of the three isolated islands of the nation of Grenada. It was not listed in the *Cruising Guide to the Grenadines*. Although, there were several hotels and many restaurants advertised.

The Captain, Andy, Barbara, and I raced full speed to the island in the dingy. We commandeered an ancient, rusty taxi and braved the narrow, rutted, steep road to the old fort, aka the hospital.

The view from the highest point on the island was breathtaking, but the hospital was badly in need of repair and a paint job.

There was a female ward, a male ward, a delivery room, the emergency room and one busy nurse.

The only physician was at a clinic on the other side of the island. The nurse said, "Not to worry. He comes at noon for emergencies."

By the time the island doctor arrived at 12:30 p.m., Andy was much better from the diuresis. His color was normal, the rales were at the base, and the tachypnea much less.

The doctor administered IV Lasix, gave him a supply of Lasix pills and potassium supplement.

There were no thick forms to fill out, no insurance forms, no detailed H+P, no extensive lab tests, xrays or disclaimers. Malpractice is not an issue in Grenada.

The only record consisted of (1) the date (2) Andy's name,(3) the diagnosis of congestive failure and (4) The treatment (40 mg IV Lasix, 60-20mg Lasix pills-60 kcl pills).

Andy made a donation of 100 EC (about $33) as the only payment for his care. He was able to sail with us to Grenada and tour the rain forest. When he returned to Kansas City he received a new metallic aortic valve.

Andy had a new parlor trick. He enjoyed holding the ladies' ear to his chest to hear the click, click, and click.

I reflected on Andy's medical experience and how inexpensive it was. Could we reduce the cost of medical care in the US of A?

(1) Make it difficult to access. The hospital was not advertised and logistically difficult to get to.

(2) Understaff it. One nurse for the hospital, and one physician spread too thin.

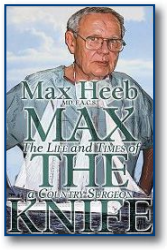
(3) Cut out the red tape. Administrative costs consume almost 30% of medical costs.

(4) Have bare-bones facility with minimal maintenance.

(5) Reform medical malpractice. Defensive medicine is a major cost to health care as well as the cost of insurance and litigation.

Would the populous of the U.S. of A. embrace all of this? Maybe? I think not!

We are spoiled, and expect the best of medical and surgical care. And we have it. **MM**



Max Heeb, MD, was a surgeon in Sikeston, Mo., before he retired in 2008 after 50 years of practice. MSMA member since 1958, he is the author of *Max the Knife* and *Surgical Imposter*. Download or purchase books at Amazon.com.
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Micro-Series: The Bite of the Loxosceles Reclusa

Viscerocutaneous Loxoscelism in an Adult with Acute Generalized Exanthematous Pustulosis

by Mark Mueller, MD, Emily Doucette, MD, Seth Freeman, MD, Amy Williams, MD & Erik Lindbloom, MD

Systemic loxoscelism may uncommonly occur with a presentation of anemia, renal failure, coma, and death.

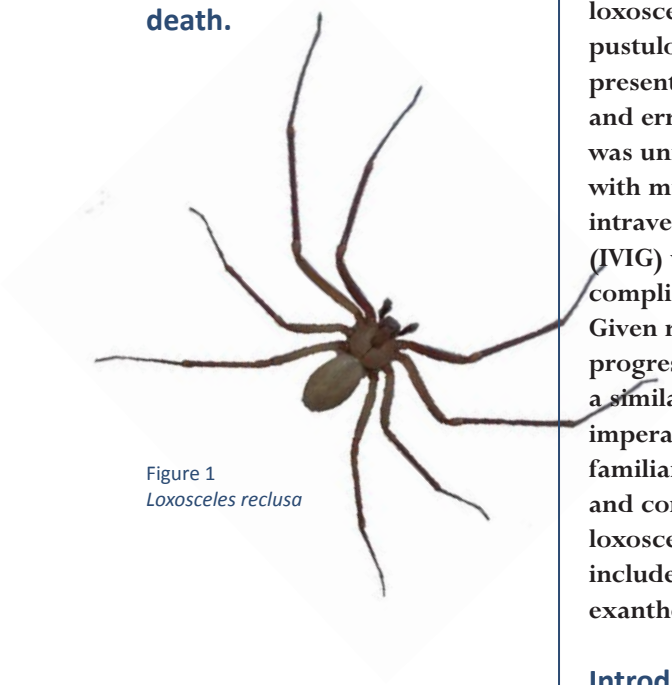


Figure 1
Loxosceles reclusa



Mark Mueller, MD, (above) Emily Doucette, MD, Seth Freeman, MD, Amy Williams, MD, and Erik Lindbloom, MD, are with the Department of Family and Community Medicine, University of Missouri.
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Abstract

This case describes an unusual presentation of a woman with viscerocutaneous (VCT) loxoscelism and exanthematous pustulosis. Due to a complex presentation resembling sepsis and errant information, she was unnecessarily treated with multiple antibiotics and intravenous immunoglobulin (IVIG) which may have complicated her course. Given recent reports of quick progression and death from a similar presentation, it is imperative that clinicians be familiar with signs, symptoms and complications of VCT loxoscelism, which can include hemolysis and acute exanthematous pustulosis.

Introduction

Loxoscelism is the clinical manifestations of a bite from any species of recluse spider, genus *Loxosceles*. *Loxosceles reclusa*, or "brown recluse" spider (BRS), is a common inhabitant of the Midwest and South Central United States and one of the few spider species in the US with a medically important bite[1] (See Figure 1). Most envenomations result in transient localized cutaneous irritation and exanthema without significant sequelae. Systemic loxoscelism may uncommonly occur with a variable presentation of anemia, renal failure, coma and death. Because BRS bites are difficult to confirm, early identification of loxoscelism can be difficult. This case report is of a young woman who presented with systemic loxoscelism and a constellation of features resembling sepsis which delayed diagnosis.

Case Report

A previously healthy, 25-year old woman of South Asian descent presented to an urgent care center with a two-day history of acute fever, malaise, and a wide-spread, erythematous, pruritic rash preceded by sore throat for two weeks. She also reported a small purple lesion on the medial aspect of her right bicep that progressed over days to include small blisters. One week prior to her presentation she was treated with azithromycin, and reportedly had a "positive strep test." She did not recall any insect or spider bites related to the lesion.

The patient met criteria for systemic inflammatory response syndrome (SIRS) and was transferred to the emergency department (ED) for further management. The patient verified that she had no recent travel and did not use tampons. She was tachycardic, tachypneic, febrile, and hypotensive. Initial laboratory results are in Table 1. She was initially started on intravenous (IV) fluids, antipyretics, and IV methylprednisolone for rash and pruritus. On admission, she had a

Table 1. Longitudinal Laboratory Values, Important Events and Antibiotics Administered During Hospitalization

	Day of Hospitalization											
Laboratory Tests	1	2	3	4	5	6	7	8	9	10	11	12
Blood Counts												
White Blood Cell Count (10^3/mcL)*	16.5/ 17.2	18.9	12.8	11.8	12.3	9.8	15.2	17.9	15.3	13.3	10.2	8.8
Hemoglobin (g/dL)	12.9/ 10.2	10.3	9.7	6.8	6.1	7.5	7.4	7.5	7.4	7.2	7.2	8.3
Post-transfusion				9.0	9.2, 8.1							
Platelets (10^3/mcL)	136/ 122	119	109	72	78	68	84	80	102	113	127	166
Hemolysis/DIC labs												
Total Bilirubin (mg/dL)	0.2	0.2		1.7	2.1	1.8	0.4	0.4	0.4	0.4		0.3
PT/INR (secs/IU)		14.8/1.0	18.4/1.4	17.4/1.3	17.7/1.3	17.8/1.3	15.1/1.1	14.9/1.0	15.1/1.0	14.5/1.0		
Lactate Dehydrogenase (u/L)					899	1348				717	657	
Fibrinogen (mg/dL)		353		423								
Fibrin Split Products (mcg/mL)		5-20 mcg										
Haptoglobin (mg/dL)				<40		<40						
Kidney/Liver Function												
Aspartate Aminotransferase (AST) (u/L)	13	18		21	27	57	77	165	212	201		120
Alanine Aminotrasnferase (ALT) (u/L)	14	15		16	16	18	32	51	84	91		113
Blood Urea Nitrogen (BUN) (mg/dL)	3	3	5	8	16	17	8	4	5	4	6	
Creatinine (mg/dL)	0.45	0.43	0.58	0.59	0.54	0.59	0.43	0.45	0.47	0.59	0.62	
Important Events			IVIG	IVIG Transfused 2u PRBCs	Transfused 2u PRBCs							
Antibiotics‡	V, D	R	R, C	R,C	R,C	R,C	R,C	V,Z	V,Z	V,Z	V,Z	V,Z

*Normal ranges: WBC (4.5-11), Hgb (12-16), platelets (150-400), Total bili (0.1-1.2), PT (12.7-15.7), INR (0.8-1.1), LDH (135-214), Fibrinogen (174-398), FDPs (<5), Haptoglobin (35-250), AST (0-32), ALT (10-35), BUN (6-20), Cr (0.5-0.95)

‡ V= Vancomycin, D=Doxycycline, R= Rocephin, C= Clindamycin, Z=Zosyn

morbilliform rash worse on both extremities at the ankles and wrists that spared the face and oral mucosa. Her right bicep had tender <1cm vesicles with surrounding erythema and ecchymosis with gravitational spread; necrosis was not seen.

Initial differential diagnoses included Loxosceles envenomation and Stevens-Johnson reaction from new exposure to ibuprofen. She was treated with antihistamines, topical steroid and general supportive measures. Antibiotics (IV vancomycin and doxycyline) were started for persistent fever. She also developed edema in her extremities, worsening leukocytosis and anemia (Table 1). In the context of a reported positive strep test, an ASO titer was drawn and IV ceftriaxone added to treat potential streptococcal toxic shock syndrome (STSS) and/or scarlet fever.

Over the next 24 hours, the morbilliform rash evolved to a monomorphic pustular rash over her entire body. She developed numbness in the right arm distal to the lesion. Tests showed increased fibrinogen degradation products and an elevated D-dimer (See Table 1). Chest CT scan showed bilateral small pleural effusions, right axillary lymphadenopathy and a possible left-sided abscess. The patient was transferred to the ICU where worsening anemia and thrombocytopenia were noted (See Table 1), as well as extensive desquamation in the pustular rash. Clindamycin was added to ceftriaxone. Two doses of IVIG were given to neutralize potential superantigens in STSS.

On hospital day four, hemoglobin fell to <7.0 g/dL and she received four total units of packed red blood cells by transfusion. She developed dark urine and was found to have Coombs positive hemolytic anemia (IgG and C3 positive, eluate negative).This was attributed to brown recluse spider envenomation or secondary to IVIG administration. IVIG was discontinued. Her arm lesion progressed to a 2x3cm necrotic patch with bullae and began to ulcerate (See Figure 2, Day 6).

Her medical records were obtained; no rapid strep test had been performed prior to hospitalization. Her hospital- drawn ASO titer returned within normal range. On hospitalization Day 6, the patient stabilized and left the ICU. She continued to be intermittently febrile. She had worsening leukocytosis, her pO2 fell to 92% and she required oxygen supplementation. Evaluation demonstrated interval development of left lower lobe pneumonia. Broad-spectrum antibiotics were again expanded to cover health care-associated pneumonia (HCAP). She clinically improved with normalizing labs and was discharged on hospital day 12 after completing treatment for HCAP. The patient's right arm continued to be swollen and painful with increasing area of necrosis, measuring 7x5 cm on day of discharge. She received a tetanus vaccination and instructions for wound care and follow up with Plastic

Figure 1
Arm lesion progressed to a 2x3cm necrotic patch with bullae and began to ulcerate by Day 6).



Surgery and Dermatology.

Discussion

Acute Loxoscelism and Necrosis

There are 11 species in the *Loxosceles* genus native to North America, with *L. reclusa* being responsible for the majority of clinically significant envenomations[1] (See Figure 1). BRS bites generally occur defensively when the spider is crushed, such as while putting on clothing, shoes or rolling over onto the arachnid while sleeping. Frequent bite locations include upper arm, thorax and inner thigh.[2]

At the point of envenomation there is minimal pain, sometimes described as "just a pinch." Pain sometimes increases to moderate or severe levels within one to two days. Envenomation results in erythema, with some patients experiencing burning pain and purpura, usually within two to eight hours. Necrosis occurs in approximately 20% of envenomations[3] and usually begins within 48 hours. A hemorrhagic, vesicular area is often surrounded by a perimeter of blanched skin, and commonly, erythema peripheral to this area. Some patients develop a concurrent pruritic, erythematous, morbilliform rash over the body thought to be caused by chemical mediators in the venom.

Necrosis is typically self-limited by 10 days post envenomation and 1-2cm in diameter at full development.[5] A venom enzyme, sphingomyelinase D, causes the local reaction by activating polymorphonuclear cells and can also degrade RBC membranes leading to hemolytic anemia. A second enzyme, hyaluronidase, causes gravitational spread of necrosis; a trait characteristic of *Loxosceles* envenomation. Healing occurs by second intention, generally within six to eight weeks.

Viscerocutaneous (VCT) Loxoscelism

A small subset of envenomated patients develop a severe reaction known as viscerocutaneous loxoscelism characterized by nausea, vomiting, high fevers and arthralgias. Over 48-72 hours, this may progress to hemolytic anemia, thrombocytopenia and disseminated intravascular coagulation. Rhabdomyolysis, renal failure and death have been reported. A first sign of this systemic reaction is a diffuse purpuric exanthema suggesting venom has entered the circulation. [6]

VCT loxoscelism has been well documented in pediatric patients with an estimated incidence of up to 16% of all envenomations.[1] In contrast, estimates of incidence among envenomated adults ranges lower, between 0.7 and 1.8%, presumably due to a lower venom/weight ratio. Pediatric cases are often more severe with high fever, rash, and Coombs positive hemolytic anemia requiring ICU admission. [7] A recent case report described an envenomated three-year old who decompensated and died in an ED setting, less than 20 hours after a known bite.[8] Pediatric and adult reports describe a diffuse pustular rash known as acute generalized exanthematous pustulosis (AGEP) developing in response to circulating inflammatory cytokines including IL-8 and G-CSF in BRS venom.[9,10] This rash can be followed by diffuse desquamation.

Hemolytic anemia associated with VCT loxoscelism is an uncommon finding, more often associated with *L. laeta*, native to South America.[11] It usually has late onset, occurring even 7-10 days following envenomation. Our patient had severe symptomatic anemia with hemoglobin dropping below 7.0 g/dL requiring multiple transfusions. This anemia resolves in children over several weeks. It is less often described in adults.[7]

Differential Diagnosis of *Loxosceles* Envenomation

Several conditions may mimic *Loxosceles* envenomation, including vasculitis, infection, and other skin conditions (See Table 2). With the increasing incidence of community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) infections, many patients present with an

Table 2. Common Conditions That May Mimic *Loxosceles* Envenomation
Vasculitis
Vascular insufficiency (diabetic ulcers)
Drug reactions (Stevens-Johnson Syndrome)
Infections (CA-MRSA, Streptococcal infections)
Contact dermatitis
Pyoderma Gangrenosum
Ertyhema Nodosum
Viral infections (herpes simplex, varicella)

abscess attributed to "spider bite."[12] The gold standard of diagnosing *Loxosceles* envenomation via spider collection occurs in clinical practice in only about 7% of cases.[13] An experimental ELISA test is available.[14-16]

A Difficult and Instructive Case

In our case, the patient's age, diffuse rash, inconsistent history and hemodynamic instability without toxic appearance and meeting of criteria for SIRS confused the presentation. The early differential diagnosis included drug hypersensitivity, *Loxosceles* envenomation, and due to errant report of positive strep test, STSS. Criteria for STSS include hypotension, temperature >40C, presence of Group A *Streptococcus*, and involvement of two organ systems,[17] which the patient met at presentation. The dependently-spreading pattern of rash, hemolysis, absence of severe systemic toxicity and lack of clear improvement with streptococcal antibiotics excluded the diagnosis of STSS and favored loxoscelism. In this case, application of the principle of Occam's razor was productive, and loxoscelism was the single cause of the entire syndrome.

Treatment of Loxosceles Envenomation

Treatment of *Loxosceles* envenomation remains controversial.[2] Supportive care includes elevation of the wound, cleansing with soap and water, general wound care, tetanus vaccination, and monitoring for secondary bacterial infection. Systemic steroids are sometimes used to control pruritus and discomfort associated with widespread rash. There is no consistent evidence to recommend using dapsone to limit necrosis, and it can exacerbate hemolytic anemia in patients with G6PD deficiency.[2] Antibiotics are rarely indicated unless a secondary cellulitis occurs. Surgical debridement is sometimes performed but has not been shown to consistently improve outcomes.

Summary

This case describes a novel presentation of a woman with VCT loxoscelism; a condition more frequently described in children. Due to a complex presentation and errant information, she was unnecessarily treated with multiple antibiotics and IVIG which may have complicated her course. Review of her hospitalization shows a temporal course consistent with VCT loxoscelism including: presenting symptoms, necrosis of wound, purpuric and pustular rashes, hemolytic anemia, DIC, and eventual resolution of symptoms. Given recent reports of quick progression and death from a similar presentation,[8] it is imperative that clinicians are familiar with signs, symptoms and progression of VCT loxoscelism in children and adults. The case presented serves to illustrate the complicated presentation with a wide differential diagnosis and challenging management needed for some cases of VCT loxoscelism.

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Disclosure

None reported.

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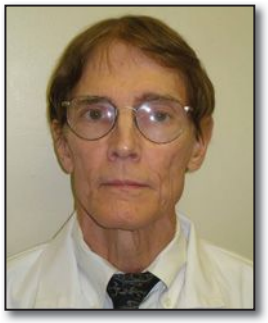


Micro-Series: The Bite of the Loxosceles Reclusa

Obtundation and Myocardial Infarction in a Case of Systemic Loxoscelism

by Karen D. Schilli, MS, Ryan K. Rader, BS, Katie S. Payne, Jonathan A. Green, PhD & William V. Stoecker, MD

This case illustrates the most severe manifestation of systemic loxoscelism: intravascular hemolysis.



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Abstract

We report an atypical course of a likely brown recluse spider bite in a 79-year-old male. The Rader scale and *Loxosceles reclusa* venom detection by ELISA provide supporting evidence for a loxoscelism diagnosis. Obtundation and myocardial infarction occurred following a drop in hemoglobin to 6.5g/dL. The rapid loss of blood volume was considered a significant etiologic factor for both the obtundation and myocardial infarction. The neurological symptoms reversed rapidly after packed red blood cell transfusion.

Case Presentation: History

A 79-year-old male presented to an emergency department with a 'sore' on his right anterior shoulder acquired during sleep. On the previous day, he noted a painful area on his shoulder, subsequently scoring the pain as 10 out of 10. On his first emergency department visit (See Timeline Day 2, Figure 1), the lesion was diagnosed as an infection and treated with trimethoprim-sulfamethoxazole. The patient was evaluated and not diagnosed with any acute additional medical conditions. Five days later (See Timeline Day 7, Figure 1), the lesion was unchanged, with pain unabated. The patient became lethargic and febrile at home. In the middle of the night on Day 7, he awoke with confusion and disorientation, unable to recognize anyone or answer any questions posed to him. On Day 8, he was admitted to the hospital with symptoms of obtundation and syncope. The patient was afebrile upon admission (98.5^{0}F) and white blood cell counts were normal (11.3 K/mm^3). The admitting diagnoses were obtundation and possible brown recluse spider (BRS) bite.

Examination by a dermatologist (W.V.S.) occurred on Day 8. The lesion on the right shoulder measured 4x6 cm. Resolving purpura was present with surrounding erythema on a background of generalized icterus (See Figure 2). The central area was marked by pallor and icterus and less than 1 cm^2 of early necrosis. Minimal gravitational spread and a faint red, white, and blue sign further indicated a BRS (*Loxosceles reclusa*) bite, also known as local loxoscelism. These positive exam findings and absence of negative exam findings fulfilled the Rader criteria[1] (See Table 1) for a BRS bite at the Likely level (see Discussion section for Rader score explanation). General examination included findings of jaundice, extreme lethargy and obtundation, disorientation to time, place and person, with the patient's friend confirming that 'he was never like this before.' Material for BRS venom determination by ELISA was obtained from the wound by saline-soaked cotton swab.

On Day 9, he was transfused with two units of packed red blood cells (PBRC). Within two hours, he was conversing normally, oriented to time, place and person. Over the course of two days, he received a total of three PRBC transfusions. On Day 10, intravenous corticosteroid therapy (methylprednisolone sodium succinate,

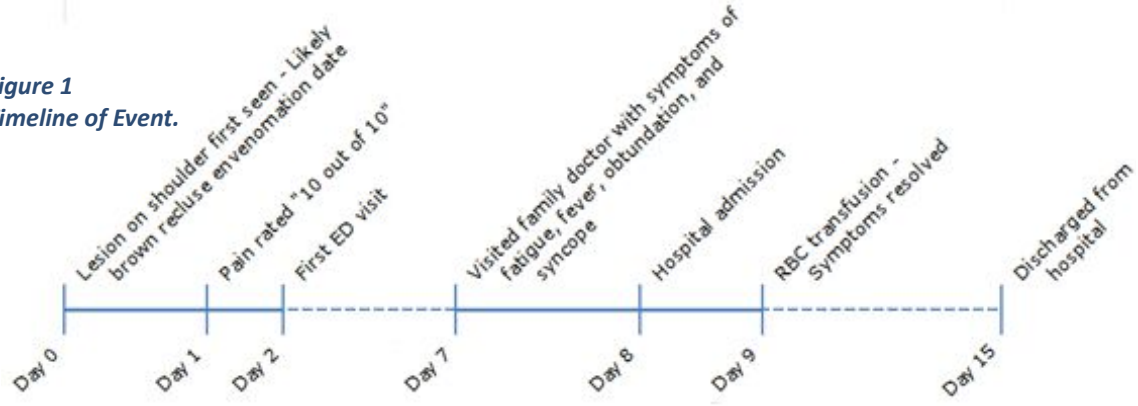
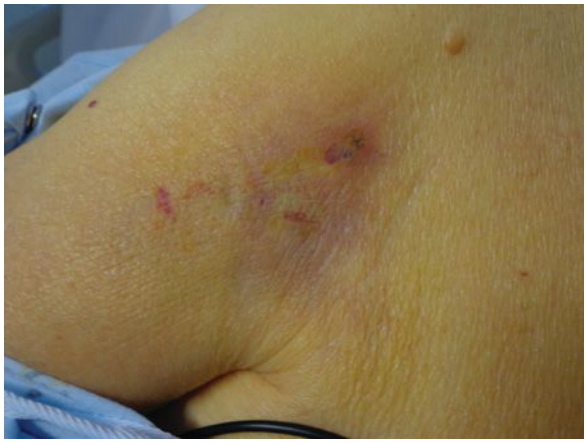


Figure 1
Timeline of Event.

Figure 2
Lesion (6x4cm) on right anterior shoulder with central bluish pallor, small area of necrosis, faint red, white, and blue sign, and minimal gravitational spread, consistent with BRS bite. Generalized jaundice was present, confirmed with total bilirubin of 8.9 mg/dL on Day 10.



80 mg/day) was initiated, later replaced with oral prednisone, 80 mg/day, with rapid tapering.

Hemolytic Anemia: Loss of Half of Blood Volume

Laboratory reports from 8 to 24 days post-BRS bite were consistent with severe hemolytic anemia. Figure 3 shows the time course of this hemolysis, persisting until nearly two weeks post-bite. The nurses noted tea-colored urine initially during his hospital stay. The hemoglobin fell to a low of 6.5mg/dL, and rose after each transfusion on Days 10-12. A peak at Day 10 and rapid decline of total bilirubin, in addition to a peak at Day 11 and a slower decline of serum lactate dehydrogenase (LDH) levels, can be seen (See Figure 3). The reticulocyte count rose to a peak of 12.2% (normal 0%-2.1%); absolute reticulocyte count rose to a peak of 0.4084 (normal 0.0260-0.0950), more than five times and four times normal levels, respectively. Urinalyses showed no occult blood on Day 3 and up to 14 red blood cells per high power field, still present on the last urinalysis, performed on Day 11. Urobilinogen levels obtained on all urinalyses were within normal limits. Fibrin degradation products remained negative.

Immunoreactivity in a tyramine-amplified brown recluse spider venom ELISA of the lesion swab was measured at 9.8 picograms (pg, 10^{-12g}). Control swab from the uninvolved control site on the opposite shoulder yielded 8.1 pg. Troponin I levels reached 6.97 ng/mL, 205 times higher than normal levels (0-0.034ng/mL). According to Ross et al.2, troponin I levels above 2.0 ng/mL represent an acute myocardial infarction with a specificity of 91%. Additionally, CK-MB levels were measured at 21.0ng/mL (Reference: 0-2.37ng/mL), indicative of a myocardial infarction. An echocardiogram during the hospital stay showed an ejection fraction of 35% (Reference: 55-70%).

Discussion

Rader Criteria for Local Loxoscelism

Many cases of localized wounds and infections have been erroneously attributed to envenomations by *Loxosceles reclusa* envenomation in the United States.[3] Numerous cases are reported in regions outside the L. reclusa habitat.[4] As yet, no reliable test has been marketed to distinguish actual *Loxosceles reclusa* envenomations from similar wounds. To help increase diagnostic accuracy, Sams et al.[5], and more recently Rader et al.[1] have developed clinical criteria to increase diagnostic accuracy. The Rader scale is a modified form of the Sams et al. score, with both systems developed to aid in the diagnosis of loxoscelism. Rader's classification system is advantageous because it takes into consideration those geographical regions inhabited by brown recluse spiders. The revised four-level classification of brown recluse spider (BRS) bite probability follows:

- **Unlikely:** Patient with subjective diagnosis, geographic location of possible bite incident outside known BRS habitat, lesion lacks features typical of BRS bites (no positive exam features).

Table 1
Features For and Against Brown Recluse Envenomations

POSITIVE EXAM FEATURES	NEGATIVE EXAM FEATURES
Lesion has small central blister without pus	Pus observed in lesion
Pale area in center of the lesion	Center raised and red
Purpura /bruising	Drainage present before one week[a]
Purpura spread in a direction consistent with gravity (gravitational spread)	Tender enlarged lymph node present[b]
Outer part of lesion is red and either pale area in center or purpura is present	Ulcer > 10 cm in diameter or more than 0.5 cm deep
	More than 2 separate lesions
Central pale area with some surrounding purpura; outer part of lesion is red (red, white, and blue sign)	Lesion present more than 3 months

[a] Ignore this negative feature for these body sites: periorbital region, hands, feet

[b] Adenopathy is observed in approximately 1% of brown recluse spider bite cases.

- **Somewhat Likely:** Geographic location of possible bite incident within known BRS habitat, lesion has one or more positive exam features.
- **Likely:** Geographic location of possible bite incident within known BRS habitat, lesion has one or more positive exam features and no features indicative of an alternative diagnosis (no negative exam features).
- **Documented:** Lesion fulfills at least one positive exam feature, BRS captured in vicinity and identified by arachnologist.

The original Sams criteria provided three grades of lesion criteria: atypical lesion, compatible lesion, and typical lesion. The Rader criteria in Table 1, revised from the Sams criteria, gives specific positive and negative exam features based on hundreds of spider bite observations (W.V.S.). The Rader diagnostic classification above also requires identification of the offending spider by an arachnologist, who must observe three pairs of eyes for definitive BRS identification. Other spiders may display dorsal violin shapes, but three pairs of eyes are unique to the *Loxosceles* genus. Our case fulfilled the Rader criteria at the Likely level.

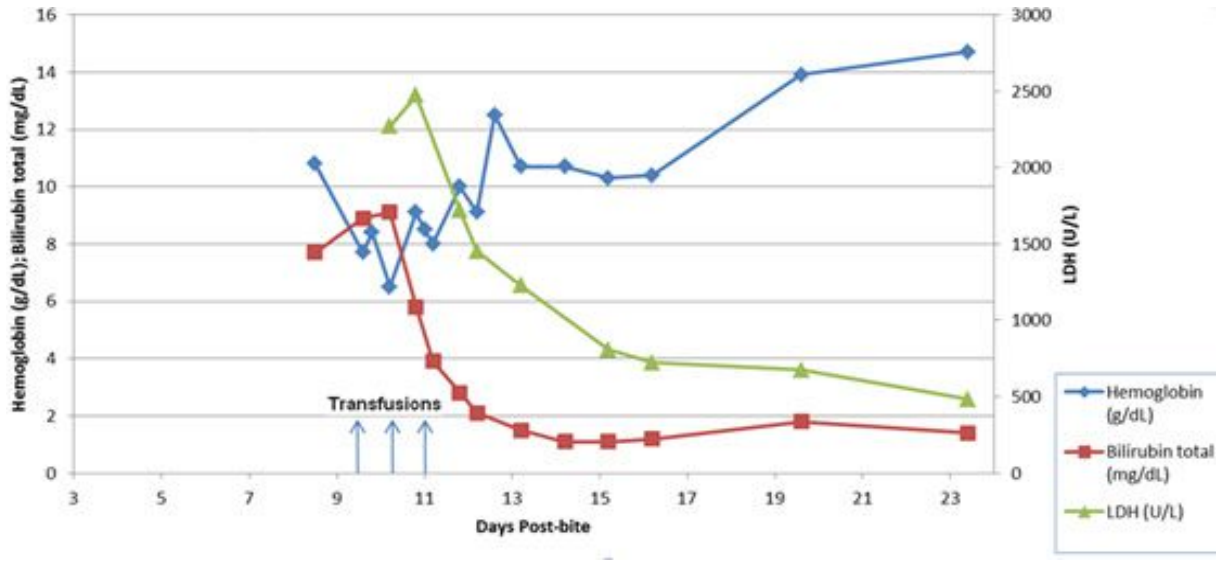
ELISA for BRS Bite Testing

Approximately 7-14% of patients bring in the spider for identification,[6] therefore most cases of likely BRS bites cannot be confirmed. An alternate method of confirmation is available using an ELISA under an experimental protocol to verify a brown recluse envenomation. As performed in Stoecker et al.,[7] the ELISA swab was performed late in this case, 10 days post-spider bite, with recovered venom from the bite site only 21% greater than the control site. The assay, currently undergoing testing prior to commercial use, shows a decreasing sensitivity after 7 days due to venom degradation; this result strengthens the argument that patients should be tested within a week of suspected envenomation. The binding of venom to skin sites is poorly understood and the use of a clinical control swab is undergoing further evaluation.

Etiology of Obtundation

The time course of obtundation was marked by the striking onset, without prior mental status changes, and sudden resolution within two hours of receiving two units of packed red blood cells. The rapid restoration of normal mental status suggested general hypoperfusion. To rule out alternative causes, two intracranial CT scans and intracranial magnetic resonance imaging (MRI) were performed. Both CT scans, 3 days and 10 days post-bite, were normal without evidence of hemorrhage or masses, and no findings to suggest an acute central nervous system event. An MRI of the neck was performed 30 days post spider-bite with severe stenosis in the bilateral proximal internal carotid arteries. The rapid return

Figure 3
Levels of hemoglobin, bilirubin, and lactate dehydrogenase. Transfusion times are noted by arrows. (Reference levels: Hemoglobin: 13.7-17.5 g/dL; Bilirubin: 0.1-1.3 mg/dL; LDH: 313-618 U/L)



to normal mental status after transfusion suggests that the rapid blood loss contributed to the mental status change. As S.C. Tindall noted, "At all times when evaluating the patient with an alteration in level of consciousness, the clinician must keep foremost in his or her mind the most common causes of coma. Leading the list are the various metabolic and toxic disturbances of the brain… Are the lips or nailbeds discolored or pale to suggest anemia or pulmonary dysfunction?"[8] Tindall also noted that "on occasion, two or more etiologies may be operating."[8] In this case, severe stenosis in the carotid arteries left the patient prone to symptoms of severe anoxia due to the drop in hemoglobin, which was restored by PBRC transfusion.

Etiology of Myocardial Infarction

The myocardial infarction was documented by increased troponin I and CK-MB levels in the course above. Diffuse coronary artery disease was documented subsequently by coronary angiograms demonstrating moderate lesions in the left anterior descending branch and the circumflex arteries. We postulate that the hypoxic stress from the reduced oxygen carrying capacity at the hemoglobin nadir exacerbated myocardial ischemia, leading to the myocardial infarction and pump failure, with ejection fraction of 35% during the hospital stay improving to 72% on the subsequent evaluation. In another potential mechanism, increased levels of plasma hemoglobin could additionally deplete nitric oxide levels leading to increases in platelet aggregation, predisposing the patient to myocardial infarction.

Laboratory Features of Intravascular vs. Extravascular Hemolysis in Systemic Loxoscelism

The destruction of red blood cells (RBCs) in systemic loxoscelism can be either intravascular or extravascular.[6,10] However, some patients present with both types of hemolysis.[10] As described by Rother et al.,[11] the destruction of red blood cells within the vascular compartment causes increased levels of hemoglobin in the plasma, in this case 7.8 mg/dL (normal 0.5-5.0 mg/dL). Hemoglobin then binds haptoglobin, and the hemoglobin-haptoglobin complex is recognized by the hemoglobin scavenger receptor, CD163 of monocytes and macrophages, which mediates the destruction of the complex and depletion of haptoglobin.[11] Findings in this case of elevated plasma free hemoglobin 7.8 mg/dL (normal 0.5-5.0 mg/dL) and decreased serum haptoglobin: <10 mg/dL (normal 30-200 mg/dL) confirmed intravascular hemolysis.

If the urine urobilinogen remains normal, extravascular hemolysis is less likely.[6] In some instances, the urobilinogen can remain normal, even in patients with extravascular hemolysis. The reporting of tea-colored urine together with the laboratory evaluation above is most consistent with primarily intravascular hemolysis.

Time Course of Hemolytic Anemia

The day of onset is not known, however no tea-colored urine was observed prior to admission. It is emphasized that late onset of hemolytic anemia is possible. In most instances, hemolysis is evident during the first week,

although hemolysis onset may appear as late as 12 days after the BRS bite.[10]

Treatment of Systemic Loxoscelism

The most severe and life-threatening complication of systemic loxoscelism is severe hemolytic anemia, which can lead to disseminated intravascular coagulation, multiple organ failure and death. Accordingly, most physicians with a patient with loxoscelism and significant hemolytic anemia will treat with systemic corticosteroids. There is no standard dose. The dose of 80 mg/day methylprednisolone sodium succinate used in this case was approximately 1 mg/kg. Systemic dapsone is sometimes prescribed for local loxoscelism, however McGlasson et al. found no beneficial effect from dapsone therapy for local loxoscelism in the New Zealand white rabbit model, which found that dapsone did not inhibit lesion formation any better than the control saline injections.[12]

Limitations

The patient received the antibiotic trimethoprim-sulfamethoxazole on Days 2-8. The possibility of sulfa-induced hemolytic anemia was considered. Neither exanthem nor eosinophilia were present to suggest drug allergy and RBC smears showed no hemoglobin precipitation (Heinz bodies) expected in sulfa-induced hemolytic anemia.[13] Hemolytic anemia due to sulfa drugs in the absence of glucose-6-phosphate dehydrogenase deficiency is an uncommon finding, yet sulfa-induced or aggravated hemolytic anemia cannot be excluded as a possibility. Blood cultures were not obtained in this case because the patient was afebrile and peripheral white blood cell count did not suggest sepsis. If sepsis is considered, every effort should be made in these cases to rule out sepsis. Features of sepsis may include mental status changes, coagulopathy, hemolytic anemia, and renal insufficiency, all of which mimic loxoscelism.

Conclusion

The case presented here illustrates the most severe manifestation of systemic loxoscelism: intravascular hemolysis, with a nadir of hemoglobin reached, in this case, ten days after the suspected envenomation. Obtundation occurred despite no prior history of mental status change and with no other cause for the mental status change found on multiple imaging studies. The obtundation was entirely reversed between one and two hours after the infusion of two units of packed red blood cells. The patient recognized his friend and was conversing with her. From that point forward, his friend was pleased that he had recovered completely, with an entirely normal mental status, confirmed by follow-up at six months. In cases where loxoscelism is suspected but no spider is found, the new Rader clinical scale and/or the experimental tyramine-amplified ELISA may help elucidate the cause of these difficult cases when hemolysis and multiple complications from the hemolysis are present.

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Disclosure

Conflict of Interest Disclosure: Dr. Stoecker and Dr. Green hold US Patent 7,927,828 for the ELISA detection of *Loxosceles reclusa* envenomation. Dr. Stoecker is also CEO and President of SpiderTek, LLC, a medical diagnostic company tasked with developing brown recluse spider traps and diagnostic assays. No other authors report any conflicts of interest. **MM**

Prescription Opioid Analgesics Increase Risk of Major Depression:

New Evidence, Plausible Neurobiological Mechanisms and Management to Achieve Depression Prophylaxis

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Our data suggest that opioid analgesics should be prescribed for a short duration and at the lowest effective dose; be exclusively reserved for severe pain syndromes; with as much adjuvants for pain management and non-narcotic analgesics as possible.



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Abstract

More than 200 million prescriptions are written annually for opioid analgesics despite limited evidence of their long-term efficacy. These medications currently are prescribed to 10% - 15% of Americans with use of long-acting opioids projected to double in the next three to four years. Despite this widespread use, little is known about the risks of opioids, particularly with chronic use. New data from our research group published in the *Journal of General Internal Medicine* provides clear evidence that prescription opioid used for non-cancer, non-HIV pain increases significantly the risk of development of major depressive disorder in opioid naïve individuals with no recent history of depression and substance used disorders. The risk of depression increased as the dose and/or the duration of opioid use increased. The purpose of the present paper is to elucidate the details of this study, to examine potential neurobiological mechanisms responsible for the depressogenic effect of opioid analgesics, and to discuss management options that emphasize depression prophylaxis.

"We accept responsibility for those past misstatements and regret they were made."
-Purdue Pharma Spokesman[1]

Introduction

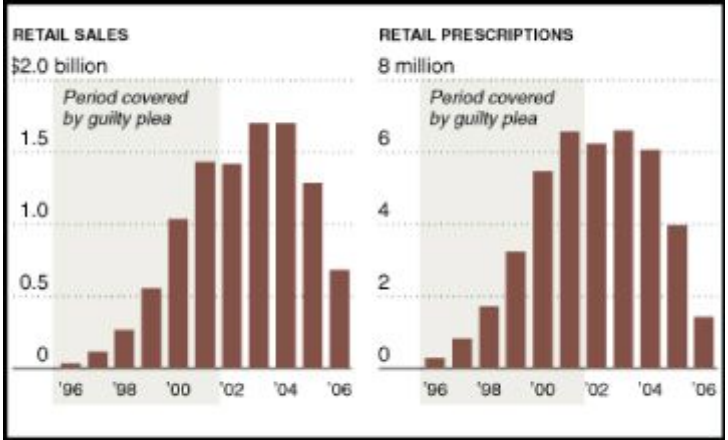
The Opioid *'Pharmageddon'*. The quote above is taken from a statement released by Purdue Pharma, the maker of OxyContin (oxycodone), coincident to its conviction in federal court in 2007 on criminal charges related to the marketing of OxyContin. The company had deliberately misled doctors and patients when it claimed and promoted this opioid analgesic as less likely to be abused than traditional narcotics. The company agreed to pay $600 million in fines to resolve the criminal charges related to "misbranding" of OxyContin. Prosecutors claimed that the fine represented approximately 90% of profits from the drug over the interval during which it was fraudulently promoted (See Figure 1).[1]

As is evident from the figure, however, the conviction had little acute impact on widespread use of or Purdue Pharma's profits from prescription OxyContin. This notwithstanding, the lawsuit against OxyContin underscores the need for a fuller understanding of the effects (both adverse and therapeutic) of

opioid analgesics. Pharmaceutical companies are not solely responsible for current widespread use of these medications. Medical professionals and patients share part of the responsibility as well. Regardless, there is little doubt that opioid analgesic use (OAU) itself has become a significant public health problem.

Despite their highly addictive potential, opioids have become a popular primary treatment of chronic non-cancer pain, such as back or joint pain. This practice has created a growing public health problem as addiction and misuse of opioids have reached epidemic proportions. Medical use of opioid analgesics has increased by a factor of 10 since the 1990s, and these drugs have become the second leading cause of accidental death in the U.S.[2] These increases in OAU occurred while the number of outpatient visits for conditions associated with chronic pain and activity limitations (e.g., arthritis) remained relatively stable.[3] According to SAMSHA, there were a total of 1.9 million new illicit users of opioid analgesics in 2012 (about 5,150 new abusers per day). Americans comprise only 4.6% of the world population, but 80% of the global consumption of opioids takes place in the U.S.[4] Due to the current high rates of abuse, the FDA is now recommending that supplies of medications containing hydrocodone be restricted to a single 90-day prescription (similar to oxycodone). Coincidentally, our research has found that prescription opioid use for more than 90 days significantly increases risk of Major Depressive Disorder (MDD), as discussed below.

Figure 1. Oxycontin Retail Sales and Prescriptions



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Terminology

Opium is one of the oldest drugs of abuse, largely due to its main natural alkaloid constituents (i.e., natural opiates), such as morphine, codeine, and thebaine.[5] Semisynthetic opiates are developed by chemical modification of natural opiates, and include heroin, hydrocodone, oxycodone, among others. The term opiate refers to a diverse group of natural or semisynthetic substances with morphine-like pharmacological activity that bind to mu, kappa, and delta opioid receptors in the body. The umbrella term opioid refers to any natural, semisynthetic or fully synthetic substance that binds to the opioid receptors, irrespective of its structural similarity with naturally occurring molecules and agonistic or antagonistic action (e.g., pentazocine, methadone, naltrexone, or endogenous opioid peptides such as beta-endorphine, among others). Opioids act upon the central and the peripheral nervous system and most have analgesic, mood altering, "sleep inducing" (hence "narcotic") effects that acting singly or in concert render them as potentially addictive. Opium also contains non-analgesic, non-narcotic, non-addictive alkaloids such as papaverine and noscapine, which act only to relax involuntary (smooth) muscles and are used to treat vasospasm, erectile dysfunction, and for cough suppression, respectively.

Understanding Causal Interactions Among Pain, Opioid Use and Depression

Depression resulting from opioid use would at first appear paradoxical, as opioids are known to have euphoric and analgesic effects. Dysphoria that occurs in $<5\%$ of exposed patients is thought to be transient and is not known to result in more serious affective illness. The tri-directional causal interactions among pain, OAU, and depression confounded attempts by researchers to determine whether opioids interposed between pain and depression could independently contribute to the development of new episodes of depression.[6] Some studies have found an increased risk of depression only in patients with opioid dependence.[7,8] Others have shown an increased risk of opioid misuse in patients with depression.[9] Also, chronic pain conditions can cause depression independent of opioid use.[10]

Advanced methods to control for bias by indication and residual confounding now allow investigators

to leverage massive medical record data including prescription records to disentangle pain from the opioid-MDD relationship. Because these data contain thousands of patients, we are able to build regression models to predict the probability of opioid receipt from hundreds of covariates resulting in propensity score. The propensity score, i.e. the probability of getting an opioid for different durations of time, is then used to weight the medical record data to balance pain diagnosis and other factors associated with opioids and depression, across opioid using patients who differ in duration of OAU. [11] Our research group employed a new user retrospective cohort design in combination with propensity score analysis and demonstrated a clear depressogenic impact of OAU, the effect detectable despite the sample (by virtue of being 85% male and 55 years of age on average and free of depression diagnosis for the first two years prior to opioid receipt) being presumably at low risk of MDD. The study is described below in detail.

Prescription Opioid Analgesics Increase the Risk of Depression

We studied the impact of new opioid prescriptions on the subsequent risk of development of depression in a large sample of patients who used the Veterans Health Administration (VA) (N=49,770)[12]. The study was the first to examine this relationship in subjects who had no recent history of MDD and no OAU (recent history was defined as 24 months prior to the beginning of the study). Propensity scores were used to control for bias by indication, and the data were weighted to balance the distribution of covariates by duration of incident opioid exposure. In other words, propensity score analyses were used to control for potential confounding effects of pain and other factors that affect exposure to opioid analgesics and the occurrence of depression. Cox proportional hazard models with adjustment for painful conditions were used to estimate the association between the duration of prescription opioid use and the subsequent risk of development of MDD. The cohort was evaluated over a seven-year interval from 2001 to 2007. The subjects ranged in age from 18 to 80, although most were middle age (mean age = 54.6 years).

Preliminary analyses indicated that incident MDD was associated with any opioid use as compared to patients who never received opioids. After adjusting for PTSD, substance use disorder, painful conditions, and socio-demographic factors in these preliminary analysis, initiating an opioid remained a significant risk factor for MDD (HR=1.51). The risk of MDD in the subjects was increased with longer duration of treatment and was dose-dependent, i.e., higher doses were associated with higher risk.

To determine if the risk for depression remained after accounting for bias by indication, we used propensity scores and inverse probability of treatment weighting to balance the distribution of covariates in patients who were prescribed opioid analgesics for 1–89, 90–180, and > 180 days, respectively, longer duration of opioid prescription was associated with increased risk of development of depression. Patients using for 90–180 days had a 25% increased risk of depression, and those using them for more than 180 days had a more than a 50% increased risk. The effects remained significant after additional adjustment for chronic pain due to neuropathies, headaches, musculoskeletal diseases, back pain, and arthritis.

We also computed the proportion of incident depression cases by high vs. low opioid dosage stratified on duration of use. Within each duration-of-use-group, patients receiving a high daily dose were at significantly increased risk of depression. However, the proportion of subjects with depression remained similar among low dose patients across duration of use. In contrast, in patients receiving a high dose, the proportion of depressed patients' increases across duration of use from 9.3% in 1–89 day users, to 13.1% in 90–180 day users to 15.0% in > 180 day users.

Although the patients were free of opioids and MDD during the two-year period before baseline assessment, it is possible that some had a remote lifetime history of MDD or had subclinical symptoms of depression that were made worse by opioid exposure. In these cases, opioid use was associated with a new episode of MDD or an exacerbation of symptoms that become severe enough to result in a diagnosis. In patients who developed MDD without a history or without subclinical symptoms of depression, opioid use was associated with a new onset of MDD. In both instances, the temporal sequence of events (opioids were prescribed first, followed by MDD) supports the hypothesis that prescription opioid analgesics may be a causal contributor to depression.

Neurobiology of Endogenous Opioids and Opioid Receptors

Our data[12] indicates that use of opioid analgesics in opioid naïve subjects without depression at the time

of opioid initiation may increase the risk of developing MDD. However, the biological mechanisms of this effect in humans have not been systematically studied. Here we review relevant molecular biology of opioids and opioid receptors.

At the molecular level, opioid analgesics act on specific opioid receptors (mu, kappa, nociceptin, or delta) with different physiological roles and functions (See Table 1).

Table 1: Opioid receptor subtypes, distribution and function.

Receptor	Subtypes & Symbols*	Endogenous ligands	Distribution	Function
delta (δ)	DOR1 DOR2 (δ1, δ2)	enkephalin	cortex hippocampus amygdala basal ganglia hypothalamus[35] nucleus accumbens[36]	analgesia antidepressant effects regulation of anxiety convulsant effects mydriasis
kappa (κ)	KOR1a KOR1b KOR2 KOR3 (κ_1, κ_2, κ_3)	dynorphin	hippocampus hypothalamus thalamus cortex caudate olfactory tubercle[37] nucleus accumbens[36]	analgesia anticonvulsant effects dysphoria reward processing response to stress miosis sedation spinal anti-nociception
mu (μ)	MOR1 MOR2 MOR3 (μ1, μ2, μ3)	β-endorphin enkephalins	thalamus reticular core nuclei periaqueductal gray of the midbrain ventral tegmentum area nucleus accumbens[36] dorsal column of the spinal cord gastrointestinal tract	euphoria reward processing analgesia spinal and supra-spinal antinociception respiratory depression response to stress regulation of the hypothalamic- pituitary-gonadal axis miosis cough suppression reduced GI motility pruritus vasodilation
Nociceptin (formerly orphanin)	NOP1	Nocipeptin / Orphanin FQ (N/OFQ)	cortex striatum thalamus hypothalamus[38] spinal cord heart lungs kidneys intestine immune cells[37]	modulation of nociception reward processing appetite regulation learning and memory regulation opioid-induced hyperalgesia

*Former nomenclature is shown in parenthesis.

Opioid receptors belong to the class of G protein coupled receptors, a large family of transmembrane receptors that react to various ligands (e.g. neurotransmitters, hormones, peptides) outside the cell and activate various intracellular signal pathways - ultimately leading to specific cellular responses.[13] The ligands that bind to opioid receptors include endogenous opioid peptides such as β-endorphin, enkephalins, endomorphins, nociceptin/orphanin, and dynorphins.[14,15] Opioid receptors and peptides are abundant throughout the brain and less so in the peripheral nervous system[16] and gastrointestinal tract. Opioid receptor-rich areas include the limbic system, hypothalamus, pituitary, and brainstem. Limbic areas of the brain are essential in modulation of mood and reward-based learning[15] both important in the neuropathology of addiction. Pharmacological agonists or antagonists at different receptors can cause a spectrum of physiological and pathological (undesired) effects,[14] both somatic and mental.

Depressogenic Effects of Opioids: Possible and Plausible Mechanisms

The mechanisms by which opioid use contributes to incident depression are not fully understood, but are likely multifactorial. In preliminary post hoc analyses, it appeared that about 25% of the cases of incident MDD were diagnosed during treatment with opioids, but in most cases incident MDD was diagnosed after the treatment ended. Several plausible mechanisms for the depressogenic effects of opioids that might account for

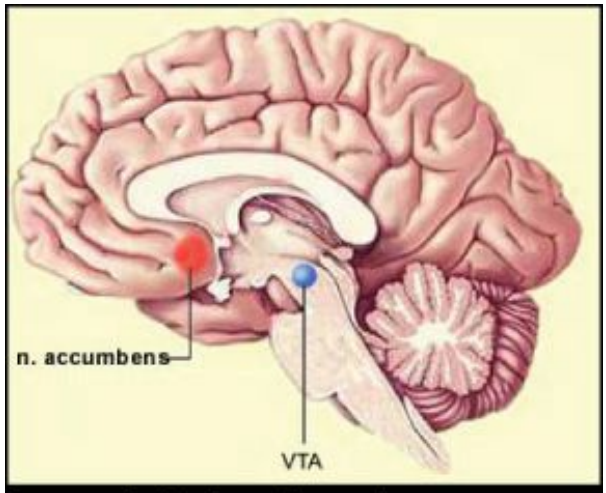


Image 1. Nucleus Accumbens and Ventral Tegmental Area

"Nucleus Accumbens" by Gustavocarra is licensed under CC SA. 3.0

both early-onset MDD occurring during opioid use and delayed-onset MDD are described below.

1. Disturbance of the brain reward system and anhedonia in the absence of opioids. The resetting of the brain "reward pathway" to a higher threshold is widely believed to be a common brain response to addictive drugs, including opioids.[17-19] The term "reward pathway" refers to a collection of brain structures that regulate behavior via the reinforcing effects of pleasurable stimuli. The neuroanatomical backbone of the reward system consists of dopamine projections from the ventral tegmentum (VTA) to the nucleus accumbens (NAc) (See Image 1) and parts of the prefrontal cortex.[17]

Opioid receptors are abundantly expressed in the NAc,[20] (See Table 1) one of the brain structures of the reward pathway, which is critical in reinforcement learning and reward.[21] Every type of reward that has been studied, including the vast majority of addictive drugs, increases the level of dopamine in the reward pathway.[18,21] Cessation of drug use frequently leads to dysphoria, anhedonia, and low motivation, all hypothesized to reflect low baseline cortical activity and low baseline striatal dopaminergic activity[22] in the absence of drugs. Such neuroplasticity could account for some cases of MDD in our sample that had occurred after opioids were stopped.

2. Epigenetic misregulation of the endogenous opioid system. Another plausible mechanism to explain our findings is opioid-induced kappa receptor hyperactivity, which has well documented depressogenic effects. Kappa opioid receptors modulate the processing of reward and reinforcement as well as some mood states,[14] among other functions (See Table 1). Empirical research in animals[23] and humans[15] implicates increased kappa receptor activity in mediation of depressed mood, in response to stress and social defeat. Opioid use leads to an early increase in CNS production of dynorphin (an endogenous kappa receptor agonist) and thus to kappa receptor hyperactivity, conceivably explaining early onset MDD in our sample. On the other hand, as drug use continues long term, a different epigenetic mechanism suppresses the production of dynorphin and thus leads to decreased kappa receptor activity.[21] Depression, body aches, and anxiety occurring for months and even years after opioid use has been discontinued ("protracted abstinence syndrome"), may be attributed to the rebound kappa receptor hyperactivity and MDD associated with the cessation of opioid treatment.[24]

3. Opioid-induced vulnerability to stress. At a system level, opioids modulate a variety of functional brain networks. For example, opioids affect the brain through their effects on the hypothalamic-pituitary-adrenal (HPA) axis and the hippocampus (a brain structure that is associated with learning, memory, and detection of novelty).[14] The hippocampus modulates the HPA axis by controlling cortisol production in response to stress. Chronic administration of morphine affects the hippocampus by decreasing the density of dendritic spines.[25] This can lead to impaired hippocampal control of the HPA axis and ultimately to depression and anxiety. Similarly, stress associated with MDD can decrease or inhibit the neurogenesis in the hippocampus and can result in atrophy of hippocampal neurons.[26] Antidepressants, however, promote neurogenesis in the dentate gyrus region[26] suggestive of potential beneficial effects of antidepressants for opioid induced depression.

4. Opioid-induced somatic correlates of depression. A spectrum of peripheral pathophysiological effects of opioids could underlie their depressogenic properties. For example, endocrine abnormalities are well recognized in chronic opioid users,[27] and include, among others, adrenal insufficiency, vitamin D deficiency, and reduced testosterone levels. Many of these abnormalities negatively affect mood[14] and clinically present with symptoms that mimic MDD, most prominently with low energy, low motivation, among others. These "physical correlates" of MDD could explain the delayed diagnosis of depression in our study.

5. Serotonergic deficit associated with opioid use. Opioids modulate several brain neurotransmitter circuits, mainly the serotonin and the dopamine networks[14] with major roles in the regulation of mood, appetite, and cognitive functions. Given the well-known role of serotonin in

mood and anxiety states, opioid induced disturbances of the serotonin system could conceivably mediate their depressogenic effects. Indeed, morphine injection in rodents releases serotonin in the limbic region, part of the brain that regulates memory and emotion.[28] However, frequent morphine injections over an extended period of time decrease serotonin activity[28], a well-documented causative factor in depression. Low serotonin activity in the context of long term opioid use may explain the correlation between increased risk of major depression and duration of use.

6. Psychosocial consequences of chronic opioid use. Although we controlled for opioid abuse and misuse, as well as for other addictions, it is possible that undetected early stages of substance use disorder could have occurred in patients using opioids for a longer period of time at a high dosages. At least some patients could have developed opioid use disorder during the trial with subsequent personal and/or adverse life events, such as low self-esteem, sense of helplessness, isolation, or family, employment, and relationship dysfunction. These are frequently seen in chronic users and may have resulted in incident diagnosis of MDD. Unfortunately, major life events and daily functioning measures are not available in medical record data and this hypothesis will be explored in planned prospective data collection.

Finally, as an unlikely possibility, acute opioid withdrawal with mood, anxiety, and physical symptoms, could have contributed to some patients receiving the diagnosis of MDD shortly after opioids were discontinued.

Treatment and Prevention of "Opioid Depression"

The treatment recommendations outlined below are drawn from our clinical experience, and the depressogenic mechanisms described above, and are offered tentatively as they need further empirical testing. Due to the likely multifactorial etiology of MDD in the context of opioid use, treatment of these patients is unlikely to be uniform. Common medical adverse effects associated with opioid use, are first to be investigated and, if identified, treated. In patients who have developed opioid-induced MDD or are considered for chronic treatment with opioid analgesics (i.e., for more than 90 days), antidepressant medications could help to prevent or treat MDD. Chronic opioid use can result in decreased serotonin activity,[28] an effect conceivably ameliorated with selective serotonin reuptake inhibitors (SSRI). As SSRIs promote neurogenesis in the hippocampus[26] their administration may help re-instate hippocampal control of the HPA vulnerability to stress[29] and prevent or treat depression in chronic opioid use. The same may hold for depression occurring after opioid use is stopped. In animal models, depressive symptoms following morphine abstinence are attenuated by fluoxetine.[30] Analogous prophylactic approach is employed with interferon therapy for hepatitis C, where antidepressants are co-administered to treat or prevent interferon induced depression with some success.[31] Whether co-administration of an antidepressant and opioid analgesics would help to prevent or delay incident depression in humans taking opioids for pain requires further study.

At least some opioid-induced depressive syndromes may have a unique underlying pathophysiology, such as overactive kappa receptors, and thus would require treatments not used in regular MDD syndromes. Buprenorphine, a partial mu receptor agonist and kappa receptor antagonist with powerful analgesic, stimulating, and antidepressant properties has been approved for opioid addiction and may prove useful for opioid induced MDD.[32,33] Due to its stimulating effects, buprenorphine may be useful in many cases of "psychomotor" depression. As a potent analgesic and a high affinity partial mu receptor agonist (making it functionally a "blocker" of full opiate agonists), buprenorphine may be an effective alternative to traditional opioids in chronic pain management with reduced risk to further expand the current opioid epidemics.

Discussion

Out of control prescription opioid use is creating a public health problem of epidemic proportions. Our study was the first to demonstrate that OAU taken as prescribed for non-cancer, non HIV pain significantly increases the risk of MDD in individuals free of depression and substance use at the initiation of opioid treatment.[12] With this in mind, practical strategies must be developed to deal with iatrogenic depression caused by long-term use of opioids for chronic pain.

The risk of incident depression increases as a function of both opioid dose and duration of treatment over 90 days. The clinical implication is that the duration of opioid analgesic use and the dose should be minimized whenever possible. In many cases, adding adjuvants for pain management makes it easier to reduce the dose and the duration of opioid treatments. Specifically, adjuvant treatment with SSRIs reduces pain severity and pain interference in opioid-dependent patients with depressive symptoms.[34] Also, alternative, non-narcotic analgesics for

acute pain syndromes may help reduce the frequency and the duration of opioid trials and thus decrease the risk of MDD.

Conclusion

Our data suggest that opioid analgesics should be prescribed for a short duration and at the lowest effective dose, be exclusively reserved for severe pain syndromes, with as much reliance on adjuvant therapy for pain management and non-narcotic analgesics as possible. We also advocate screening for depression and substance use disorder for all patients during opioid trials. Practitioners should consider antidepressant prophylaxis and treatment of MDD in patients entering chronic opioid treatment. More research is needed to determine whether co-administration of anti-depressants and opioids would help to prevent incident depression in humans taking opioid analgesics.

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Disclosure

None reported.

MM

Missouri State Medical Association Balance Sheet 2013

ASSETS		LIABILITIES AND NET ASSETS	
CURRENT ASSETS:		**CURRENT LIABILITIES:**	
Cash and Cash Equivalents	$ 774,921	Accounts Payable and Accrued Expenses	$ 14,985
Certificates of Deposit	203,889	Accrued Vacation	68,325
Short-Term Investments	8,300,725	Deferred Revenue	31,097
Interest Receivable	167	Deferred Dues	804,136
Accounts Receivable	5,649		
Accounts Receivable - Insurance Agency	16,683	Total Current Liabilities	918,543
Prepaid Expenses	12,270		
Total Current Assets	9,314,304		
FIXED ASSETS:		**NON-CURRENT LIABILITIES:**	
Land	83,000	Non-Qualified Deferred Compensation Agreement	368,199
Building and Improvements	605,077	Pension Benefit Liability	(81,976)
Furniture and Equipment	275,590		
Less: Accumulated Depreciation	(824,012)	Total Non-Current Liabilities	286,223
Total Net Fixed Assets	139,655	Total Liabilities	1,204,766
OTHER ASSETS:			
Note Receivable - MSMA Ins. Agency	209,610		
Investment in Subsidiary - MSMA Insurance Agency	(276,188)	**NET ASSETS:**	
Certificates of Deposit	104,305		
Long-Term Investments	2,502,262	Unrestricted	10,789,182
Total Other Assets	2,539,989	Total Net Assets	10,789,182
TOTAL ASSETS	$ 11,993,948	**TOTAL LIABILITIES AND NET ASSETS**	$11,993,948

Missouri State Medical Foundation 2013

ASSETS		LIABILITIES AND NET ASSETS	
CURRENT ASSETS:		**LIABILITIES:**	
Cash	$ 305,130	Funds Held for Others	$ 142,184
Investments	64,135		
Notes Receivable - Current	476,100	**TOTAL LIABILITIES**	142,184
Accrued Interest	182,398		
Total Current Assets	1,027,763		
EQUIPMENT:			
Office Equipment	1,608		
Software	10,692		
Less: Accumulated Depreciation	(12,300)		
Total Net Fixed Assets	-		
NON-CURRENT ASSETS:			
Investments	2,950,545		
Total Non-Current Investments	2,950,545		
Notes Receivable - Long Term	2,300,778	**NET ASSETS:**	
Allowance for Doubtful Accounts	(163,106)	Unrestricted	5,973,796
Notes Receivable - Long Term (Net)	2,137,672		
TOTAL ASSETS	$ 6,115,980	**TOTAL LIABILITIES AND NET ASSETS**	$ 6,115,980

Missouri Physicians Health Foundation 2013

ASSETS

CURRENT ASSETS:		
Cash and Cash Equivalents		
Cash - Checking	$	100,824
Cash - McIntosh Fund		27,120
Mutual Funds - McIntosh Fund		5,005
Certficates of Deposit		215,000
Accounts Receivable		161,090
Allowance for Doubtful Accounts		(21,551)
Accrued Interst		41
Total Current Assets		487,529
NON-CURRENT ASSETS:		
Investments - McIntosh Fund		16,963
Property and Equipment		
Office Furniture and Equipment		51,924
Less: Accumulated Depreciation		(27,560)
Net Property and Equipment		24,364
Total Non-Current Assets		41,327
TOTAL ASSETS	$	528,856

LIABILITIES AND NET ASSETS

CURRENT LIABILITIES:		
Accounts Payable	$	1,614
Total Current Liabilities		1,614
NET ASSETS:		
Unrestricted		527,242
Total Liabilities and Net Assets	$	528,856



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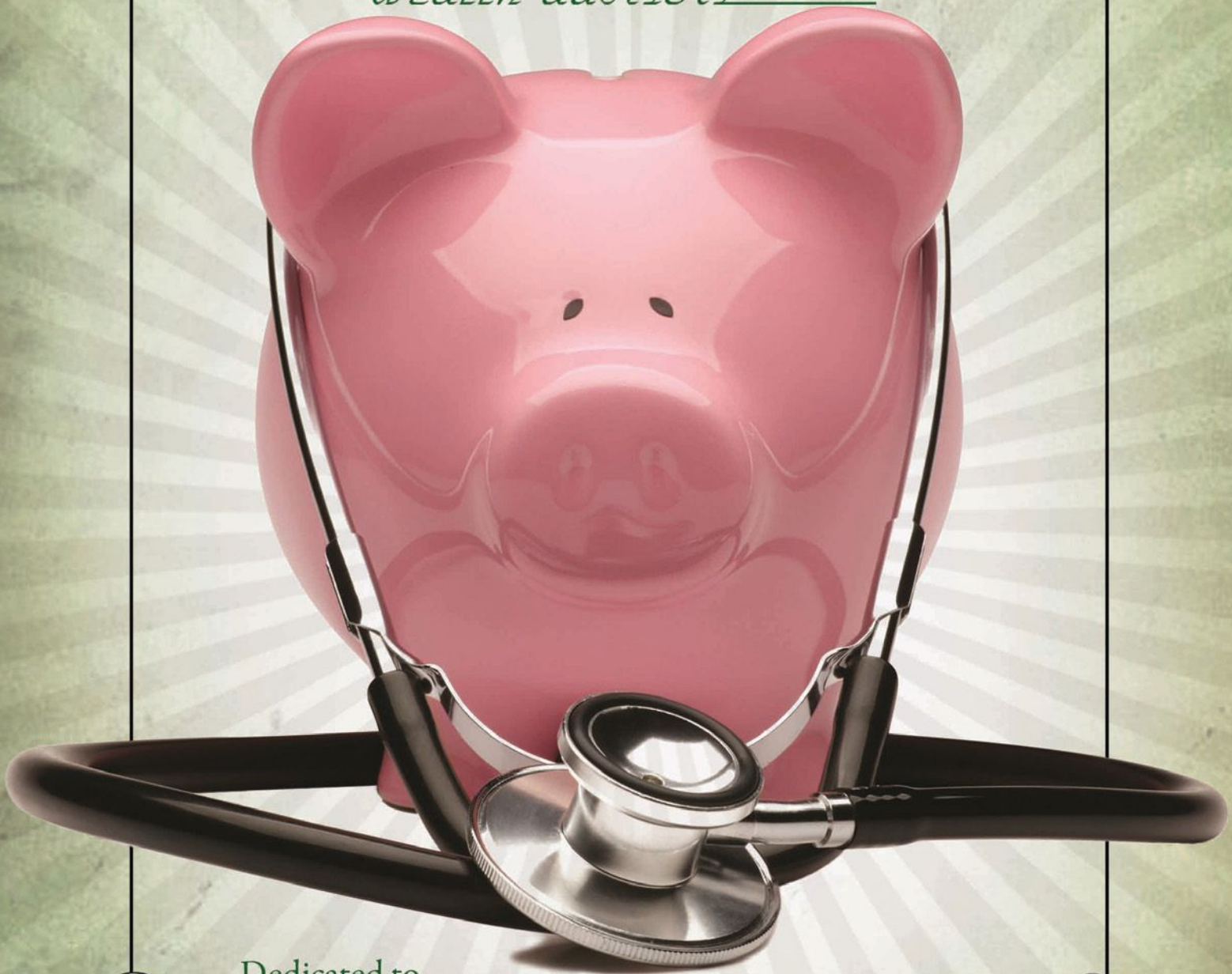
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