Volume 10 • No.1 2016

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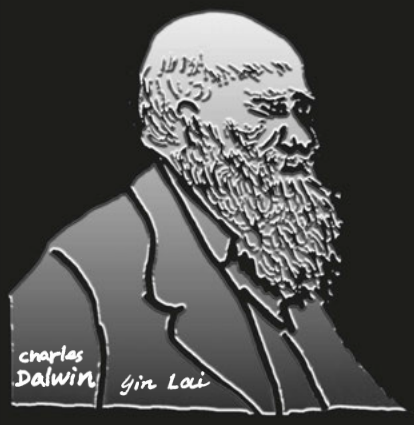

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Our Mission and Purpose

Southern California Clinicians was established by the Medical Staff of Pomona Valley Hospital Medical Center in Pomona, California. It provides a journal for modern California clinicians to publish articles to share their clinical experiences and opinions with other physicians, show their academic achievements in medical practice, and keep a permanent record of valuable case studies and case reports from all departments and all specialities in the modern era.

This journal invites all clinicians in southern California to contribute interesting articles and reviews, including new developments in clinical skills and techniques, or new procedures applied during their medical practice.

In order to maintain the highest quality, accuracy and academic dignity, we reserve the right to peer review all articles. Articles will be reviewed by our editorial board and special consultants.

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Special Thanks

Richard Yochum, President and CEO of Pomona Valley Hospital Medical Center

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Felice Loverso, President and CEO of Casa Colina Hospital and Centers for Healthcare

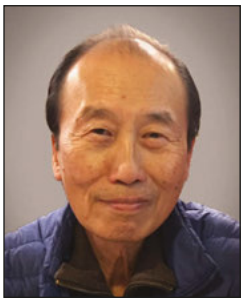
Guidelines for Authors

On behalf of the editorial staff of the medical journal *Southern California Clinicians*, I would like to extend an invitation to you to contribute articles for publication. Articles that pertain to your medical practice, any case reports you may have, or your past clinical experiences are welcome. Articles for publication in the 2017 edition are due no later than April 30th, 2017.

1) Use a single page to show your full name, your academic degrees and affiliations, and your current address, phone number, fax, e-mail.
2) All articles must be titled.
3) Please write your article with Microsoft Office Word, double spaced.
4) Length is flexible, from 1 page to 10 pages.
5) You may include a short abstract and conclusion as you wish. Slides, tables, figures, photos or pictures are welcome. Most important is a list of references numbered in the order in which you marked in the text.
6) All articles have to be original, never been published before, reflecting your own experience, knowledge and opinion.
7) All articles, once accepted, will be peer reviewed, corrected or revised and will be sent back to you for your approval.
8) Please submit all articles in both Microsoft Word format and pdf format by email to Yin H. Lai, M.D. at his email address: yinhlai@gmail.com

Preface for this Edition

Yin H. Lai, M.D.
Editor-in-Chief



10TH ANNIVERSARY OF SCC

The medical journal, Southern California Clinicians with its gala edition published in 2003, was initially supported mainly by the president/CEO Richard Yochum of Pomona Valley Community Hospital and some local clinical practitioners. Later on, as medical staffs from San Antonio Regional Hospital, Casa Colina Hospital and Centers for Healthcare, and Western University of Health Sciences have been contributing the journal by writing articles, this medical journal became a place to show the academic achievement of those medical organizations.

In this 10th anniversary issue, we are proud of excellent articles authors who are associated as faculties with USC Keck School of Medicine, UC Irvine School of Medicine, Western University School of Medicine in Pomona, California State Polytechnic University, San Francisco State University, Casa Colina Hospital and Centers for Healthcare, San Antonio Regional Hospital, Pomona Valley Hospital Medical Center, City of Hope Cancer Center, and Arrowhead Medical Center in Colton, CA.

Every article in this issue is important and interesting to all medical community. One example is Dr. Maurer's "Mindfulness". The study of "Mindfulness" was originated from Jon Kabat-Zinn, Ph.D. at University of Massachusetts Medical School. In 1979, he founded Mindfulness-Based Stress Reduction Clinic(MBSR) which has now become nationwide. The MBSR program has been promoted by NIH. In Southern California alone, we can participate in the MBSR program at UCI, UCLA, UCSD. Why is it so popular? Once you read this article, you will understand.

While I can not introduce all articles on this page, all of them are strictly peer reviewed and I recommend all articles to be read because they are so important to all practicing clinicians in taking care of patients today.

I want to thank all article reviewers and entire editorial board members who spent valuable time to make the publication possible. I want to thank all article contributors who borrowed many weekends and nights from their families in order to write the high quality articles for publication.

At last, I shall express my heartfelt thanks to all generous supporters President/CEO Richard Yochum of Pomona Valley Hospital Medical Center, President/CEO Harris Koenig of San Antonio Regional Hospital, President/CEO Felice Loverso of Casa Colina Hospital and Centers of Healthcare, Western University Patient Care Center, Chaparral Medical Group, Femcare OB-GYN Associates of Pomona/Ontario/Chino Hills, INI (Inland Neurosurgery Institute) Nephrology Associates of Pomona and Upland, Alinea Medical Imaging of Pomona/Santa Ana, Stanley Kim Hematology and Oncology Clinic, Martin J. Porcelli, D.O., ABC Pharmacy, Whitefield Lab/X-Ray and many other individual clinicians.

POST-RENAL TRANSPLANT ERYTHROCYTOSIS
A Case Report

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Introduction

Renal transplants are associated with a wide variety of short term and long term complications; one such complication is posttransplant erythrocytosis (PTE) which occurs in 8-15% of patients (1-4). The diagnosis of PTE can be made based on elevated hemoglobin (>17 g/dL) and/or hematocrit (>51%) that persists for more than six months following renal transplant. In addition, other causes of erythrocytosis must be ruled out such as malignancy, pulmonary hypertension, or chronic obstructive pulmonary disease, as well as the presence of other blood disorders (e.g. thrombocytosis, leukocytosis) (1-5).

The development of PTE is dependent on numerous risk factors including: male gender, smoking status, diabetes, retained native kidneys, rejection-free course, use of cyclosporine and preserved GFR (2, 5, 6). While other risk factors such as end stage renal disease, polycystic kidney disease, glomerulonephritis, and renal artery stenosis have been suggested in early case reports, these risk factors have not been confirmed in subsequent studies (2, 6).

Despite these risk factors, the pathogenesis of PTE is not well known. Some suggested mechanisms are dysregulation of hormones and growth factors such as erythropoietin, insulin-like growth factor-1 (IGF-1) and its associated binding proteins, the renin-angiotensin-aldosterone system (RAAS), and androgens (10-12). While some patients with PTE have inappropriately high levels of erythropoietin, PTE can also be present with normal concentrations of erythropoietin (1, 7). Activation of the RAAS may also lead to increased levels of erythropoietin, leading to erythrocytosis (9). IGF-1 concentrations have also been found to be elevated in patients with PTE, though the mechanism is unknown (8, 17).

The clinical manifestations associated with PTE are similar to those associated with other forms of erythrocytosis. Approximately 60 percent of patients experience malaise, headache, plethora, lethargy, or dizziness, while 10 to 30 percent experience thromboembolic events. Rarely, death can occur in 1 to 2 percent of untreated patients (2). 86% of patients develop symptoms and are diagnosed within the first 24 months following the transplant (5).

Treatments with medications such as ACE inhibitors and ARBs are considered first line therapies because they are typically well tolerated and have less adverse effects than other treatments. While the exact mechanism is unclear, these drugs are geared towards suppressing the renin-angiotensin system (RAS) and have proven effective in a number of patients (1, 2, 13). Previous studies have demonstrated that ACE inhibitors and ARBs are associated with a decrease in erythropoietin plasma concentration, though these drugs have also been found to reduce hematocrit in the absence of significant decrease in erythropoietin plasma concentrations (1, 13, 14).

Case Report

The patient was referred to our clinic on January 9, 2015 as a 60 year old African American male with a history of hypertension diagnosed in 1997. He received a kidney transplant in 2000 due to chronic renal failure, secondary to hypertension. His other past medical history includes gout, prostate cancer status post prostatectomy, and chronic kidney disease stage III. The patient also reported allergies to micardis, tacrolimus, and mycophenolate sodium. The patient admitted to a history of erythrocytosis since July 2014 and was placed on Lisinopril to correct his hemoglobin and hematocrit; however, he could not tolerate the treatment due to cough and was discontinued from the ACE inhibitor. He was then placed on Losartan but reported an allergic rash to this medication and the ARB was discontinued.

At initial presentation, the patient had lab values of WBC 7,400, platelets 135,000, hemoglobin 17.2 g/dL and hematocrit 54%. Additional testing revealed a negative JAK-2 V617F mutation, thus ruling out polycythemia vera. Since no other cause of erythrocytosis could be identified, the patient was diagnosed with posttransplant erythrocytosis. Because of the patient's adverse responses to ACE inhibitors and ARBs, phlebotomies were recommended to maintain the patient's hemoglobin below 17 g/dL.

Discussion

Based on the patient's history of kidney transplant in 2000, the erythrocytosis is most likely a complication of this procedure given that the serum lacked a JAK-2 mutation and the patient's white blood cell and platelet counts were within normal limits. The majority of post-renal transplant patients develop erythrocytosis in the first 24 months following transplant (5). However, our patient has an atypical presentation in which his erythrocytosis developed approximately 13 years after transplant. While PTE was reported in approximately 19 percent of patients 25 years ago, the incidence has decreased, averaging 8.1% since 1997 (4). In addition, PTE will spontaneously remit in one-fourth of patients within two years of onset if left untreated. Likewise, remission has also been seen as a consequence of deteriorating kidney function from chronic rejection (18).

Treatment

Patients who display a hemoglobin <18.5 g/dL but >17 g/dL are started on Losartan 50mg/day and the dose is increased until the hematocrit has been successfully lowered. However, in those with hemoglobin > 18.5 g/dL, phlebotomy + ARB/ACE inhibitor are recommended (19). Therapies are usually indefinite due to relapse toward pretreatment levels in the majority of patients. Other available treatments are Theophylline, antiproliferative agents such as Azathioprine, Mycophenolate, MTOR inhibitors such as Sirolimus and Everolimus, and a serotonin 5-HT2 receptor antagonist, Ketanserin. While these other medications will decrease the hemoglobin and hematocrit, they are accompanied by numerous side effects (3, 4, 15, 16, 20).

Since the patient was unable to tolerate Lisinopril or Losartan treatment, the treatment with phlebotomies was recommended. The other available treatments were not recommended due to consequences of more adverse drug reactions. Compared to first-line treatment options, phlebotomies carry a risk of severe iron deficiency anemia and must be closely monitored with labs as part of the maintenance therapy. The patient is currently being monitored regularly at approximately 4-week intervals with CBC and iron studies. If the patient's labs reveal elevated hemoglobin (>17g/dL) then the patient is scheduled for phlebotomy. The patient is currently performing well, has well preserved graft function, and has not developed any complications from PTE or phlebotomy treatments.

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HISTONE DEACETYLASE INHIBITORS AS FUTURE DISEASE-MODIFYING THERAPY FOR HUNTINGTON'S DISEASE

Synopsis Review

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Huntington's disease (HD) is a autosomal dominant fatal neurodegenerative disorder affecting 5 to 10 per 100,000 worldwide [1], manifesting as chorea, dementia, and psychiatric symptoms due to degeneration of GABAergic medium-size spiny neurons (MSNs) in the striatum and pyramidal neurons in cerebral cortex [2] Abnormal expansion of CAG triplet repeats in the first exon of the huntingtin (HTT) gene on 4p leads to a mutant HTT protein with a poly Q tract, which forms polyglutamine aggregates, binding to caspase 2 [3], resulting in intracellular ubiquitin-positive inclusions and ultimately neuronal death [4].

There is a 'gray zone' of incomplete penetrance with 36-40 repeats, but with 41 or more repeats it is 100% penetrant.

There are very few neurogenetic disorders (for instance, myotonic dystrophy or Friedreich's ataxia), where the molecular pathogenesis has been this well-elucidated. This serves as a strong foundation for therapeutic targets of the disease.

Currently there is no cure and only one FDA approved medication, namely Xenazine® (tetrabenazine), which is used to treat the chorea but not the dementia, which is the most debilitating symptom [5].

Furthermore, also included in the package insert of Xenazine® is the increased risk of suicidal ideation in a condition where suicide rates are already high [6].

Recently histone deacetylase (HDAC) inhibitors have been proposed as potential therapeutic targets for HD [7].

The pathogenesis of HD lies at the post-translational modification level by histones. Post-translational modifications of upstream binding factor (UBF) are affected by histone acetyltransferase [8].

McFarland et al. found decreases in the number of sites occupied by acetylated histone H3 (AcH3) in the striatum of transgenic R6/2 mice, the mouse model for HD [9]. Patients with HD were also found to have loss of AcH2A, AcH2B, AcH3 and AcH4 expression in the caudate nucleus and cerebellar Purkinje cells [10].

Furthermore, treatment with HDAC inhibitors was found to increase global AcH3 levels with concomitant increases in transcript levels [11]. Such HDAC inhibitors were also found to reduce levels of H2A histone family, member Y (H2AFY) in a randomized phase II clinical trial [12].

To date, there are over twenty HDAC inhibitors have entered clinical studies and two of them have already reached the market as FDA-approved treatment of cutaneous T-cell lymphoma (CTCL), namely the hydroxamic acid derivative SAHA (vorinostat, Zolinza®) and the cyclic depsipeptide FK228 (romidepsin, Istodax®) [13] .

Other HDAC inhibitors include Lithium (which was shown to down-regulate HDAC1) [14], EVX001688 [15], and valproic acid [16].

Perhaps the most interesting compound is histone deacetylase (HDAC) inhibitor 4b, which preferentially targets HDACs 1 and 3 via ubiquitin-proteasomal and autophagy pathways [13] and ameliorates HD-like phenotypes in transgenic mice and Drosophila, suggesting their potential use for human HD [17].

What is the role of HDAC3 in HD? Neuroprotection by normal HTT protein is achieved by sequestering histone deacetylase-3 (HDAC3), which promotes neuronal death. In contrast to the normal HTT protein, mutant HTT protein interacts poorly with HDAC3. Therefore, expression of mutant HTT protein liberates HDAC3 from HTT, thus de-repressing its neurotoxic activity [18]. HDACs themselves are known to be critical regulators of DC lineage commitment and development [19].

Already it has been over 140 years since George Huntington has first described this condition [20], with the causal gene found only within the last 20 years [21]. Perhaps there will be a disease-modifying drug within the next 20 years. Large-scale, phase III randomized placebo-controlled trials should be the next chapter in HD.

Acknowledgement: none

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ON PHYSICIAN BURNOUT —A SERIOUS PROBLEM!

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Burnout among US physicians is getting worse. An update from a three-year study evaluating burnout and work-life balance shows that American physicians are worse off today than they were three years earlier.[1]

It has been reliably estimated that on average the United States loses as many as 400 physicians to suicide each year (the equivalent of at least one entire medical school).[2]

Both in the medical and mainstream literature, articles on physician burnout, depression and suicide have proliferated in recent years drawing greater and alarming attention to the well-being of physicians and medical trainees.1-13 In 2015 there was a record number of publications on this topic. Sadly, much of this focus has been spurred by more publicized reports of burnout and the suicides of residents and physicians.2, 4-5, 7, 12-13 The intent of this article is to provide a brief overview of the problem and list available resources.

Professional burnout is a syndrome defined as emotional exhaustion, cynicism, perceived clinical ineffectiveness, and a sense of depersonalization in relationships with coworkers, and in the case of health care providers, patients, or both.14 It can be measured in various ways most often by use of the Maslach Burnout Inventory.14

In Medscape's 2015 annual Physician Lifestyle Report,15 those who responded that they were burned out increased from 39.8% in 2013 to 46% over a two year period. The highest burnout rates were found in critical care (53%) and emergency medicine (52%) with half of all family physicians, internists, and general surgeons reporting burnout. In another national study of physicians, using the Maslach Burnout Inventory, burnout rates were reported as ranging from 30% to 65% across specialties, with the highest rates of burnout incurred by physicians at the front line of care, such as emergency medicine and primary care physicians.6Almost 46% of physicians reported at least 1 of the 3 symptoms of burnout. Just over 40% of physicians surveyed did not think their work schedule left enough time for personal or family life.

The Medscape 2016 survey16 in comparing burnout rates between 2011 and 2014, observed an increase from 45.5% to 54.4% in the percentage of physicians reporting at least one burnout symptom. Many physicians commented anecdotally on factors that contributed to burnout; the most frequently noted were insurance issues. Other oft cited causes were threat of malpractice, the change to the 10th edition of the International Classification of Diseases (ICD-10), lack of patient respect and appreciation, and more personally, family stress. Computerization was cited as a significant cause of burnout in the 2015 Medscape survey. Babbott et al. found that primary care physicians with the highest number of electronic medical record functions also experienced the highest amount of stress.17

Burnout imperils the triple aim of enhancing patient experience, improving population health, and reducing health care costs. Burnout has been shown to negatively effect patient care18 and is associated with lower patient satisfaction, reduced health outcomes, and possibly increased costs.19 Many of the factors that lead to burnout are also associated with a higher likelihood of physicians reducing their work hours or leaving their practice.6 Over time, burnout and low satisfaction predicted reductions in full-time work.20 Care of the provider has been proposed as a quadruple aim of health care.3

Physician author, speaker and consultant on physician burnout, Dike Drummond, MD, CEO, TheHappyMD.com states that "there is an epidemic of physician burnout in the United States, and that it has a pervasive negative effect on all aspects of medical care including [your sic] physician career satisfaction." Drummond9 describes medical practice as the classic high-stress combination of great responsibility and little control. Being able to control work hours has increasingly been found to play an important role in reducing stress and, therefore, burnout among physicians.9-1, 17

In his series of three articles in Family Practice Management,9-11 Drummond points out that burnout is directly linked to the following undesirable consequences: Lower patient satisfaction and quality of care, higher medical error rates and malpractice risk, higher physician and staff turnover, physician alcohol and drug abuse and addiction and physician suicide.

Rates of suicide are higher in physicians than in the general population4 with studies indicating that job stress is a factor.5 The profession has one of the highest rates of suicide.20 It can be reasonably assumed that underreporting of suicide as a cause of death occurs among physician families and communities.2 Depression is a major risk factor in physician suicide. Other risk factors include the presence of bipolar disorder and alcohol and substance abuse. While burnout and depression are considered distinct entities, they are interrelated and can overlap considerably. In a study among surgeons, there was a strong correlation between indicators of burnout and depressive symptoms with the incidence of suicidal ideation.21

In a special section devoted to physicians, the following statistics are published by the American Foundation for Suicide Prevention (AFSP).20

Facts about physician depression and suicide

- Each year in the U.S., roughly 300–400 physicians die by suicide.
- In the U.S., suicide deaths are 250–400 percent higher among female physicians when compared to females in other professions.
- In the general population, males complete suicide four times more often than females. However, female physicians have a rate equal to male physicians.
- Medical students have rates of depression 15 to 30 percent higher than the general population. Women physicians have a higher rate of major depression than age-matched women with doctorate degrees.
- Contributing to the higher suicide rate among physicians is their higher completion to attempt ratio, which may result from greater knowledge of lethality of drugs and easy access to means.
- Women physicians have a higher rate of major depression than age-matched women with doctorate degrees.

Struggles with depressive symptoms, sleep deprivation, inadequate recovery from heavy workloads and increasing administrative tasks begin early in the physician career often in medical school and residency.

Depression in Medical Trainees

In their meta-analysis spanning the 50 year period from 1963 through 2015, and having extracted 31 cross-sectional and 23 longitudinal studies, Mata et al, found that in resident physicians, the overall pooled prevalence of depression or depressive symptoms was 28.8%.7 Prevalence estimates ranged from 20.9% using the 9-item Patient Health Questionnaire to 43.2% using the 2-item PRIME-MD. Most striking was an increased prevalence of depressive symptoms with each increasing calendar year. No statistically significant differences were observed between studies that were cross-sectional versus longitudinal, of interns versus upper-level residents, or nonsurgical versus surgical residents.

In the editorial accompanying this study,8 Schwenk enumerates factors which are likely to contribute to the generational findings. These include being in an era of life-prolonging and life-creating technologies that lead to difficult ethical dilemmas, risk-based reimbursement strategies, the use of and demand of electronic medical records and documentation requirements, malpractice exposure during residency, short hospital lengths of stay with sicker patients reducing opportunity for thinking and learning, direct-to-consumer advertising that causes patients to demand medications for conditions they sometimes do not even have, and online ratings of physician performance.

Schwenk proposes 3 categories of solutions to this: provide more and better mental health care to depressed physicians and those in training, limiting trainees'

exposure to aspects of the training environment thought to contribute to some degree to poor mental health, and reflect on the possibility that the medical training system needs more fundamental change. Schwenk critiques each of these proposals highlighting high levels of stigma attached to seeking mental health care and the efforts of the Accreditation Council for Graduate Medical Education (ACGME) requirements22 limiting the duty hours for physicians in training to reduce resident stress, burnout, sleep deprivation, and medical errors.

Despite the 2011 ACGME efforts (which built on the first phase in 2003) to restrict work hours, there were no significant changes reported by interns in hours slept, depressive symptoms or wellbeing scores. In addition, concerns about making a serious medical error increased.23 To conform to the restriction that interns not work more than 16 hours per day, many programs instituted a night float system, which created other challenges perhaps inadvertently undermining some of the ACGME goals. Without hiring additional clinical staff/ trainees, the ACGME reforms may have exacerbated the problem of work compression with the same number of residents expected to complete the same work in less total time.23

Cultural and Institutional Challenges

Physicians have unique barriers to obtaining mental health care including the fear of temporary withdrawal from practice, of lack of confidentiality in treatment and concern about negative consequences with licensing boards and credentialing processes.

The culture of medicine with its deeply ingrained values of stoicism and hard pushing through heavy workloads and fatigue, a desire to appear healthy, invulnerable and in control contribute to a lack of awareness of levels of personal problems and work against help-seeking more physical ailments let alone stress-related and/or emotional ones.

While there have been efforts to boost physician resilience to workplace stressors,24 many have been firm in their data driven recommendations that it is institutional and federal mandates that require fundamental change. In their article, 10 Bold Steps to Prevent Burnout in General Internal Medicine, Linzer et al.25 propose an institutional quality improvement agenda to both prevent and lower rates of burnout. These steps include establishing institutional metrics of physician satisfaction and well-being, improving work conditions, focusing on career development and self-care. The authors state that "any system that does not measure, monitor and optimize clinician well-being and sustainability is at risk."

Shanafelt et al6 state, "the fact that almost 1 in 2 physicians has symptoms of burnout implies that the origins of this problem are rooted in the environment and care delivery system rather than in the personal characteristics of a few susceptible individuals. Policy makers and health care organizations must address the problem of physician burnout for the sake of physicians and their patients."

Summary

Addressing physician burnout is a national imperative.6 The prevalence of physician burnout is at an alarming level. There is now a preponderance of evidence of the problem. When and how institutional reforms will unfold is uncertain. What will be the toll for the medical profession and the health care system? What is the price that physicians and their families are paying? The clarion call has been sounded.

Essential Reading

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Grinspoon, P. How to treat a drug-addicted doctor. Los Angeles Times, June 8, 2016. http://touch.latimes.com/Accessed on 6-8-16.

Oaklander, M. Life support: Inside the movement to save the mental health of America's doctors. Time Magazine, September 7-14, 2015 43-50.

Resources

Physician Health and Well-Being Committees at all JCAHO (Joint Commission on Accreditation of Health Care Organizations) accredited hospitals

California Public Protection and Physician Health (CPPPH) - http://www.cppph.org/

CPPPH's mission is to support a healthy physician workforce in the state of California. CPPPH is dedicated to enhancing patient safety by developing programs that assist health professionals who identify, refer, treat, and monitor physicians with potentially impairing conditions.

Pacific Assistance Groups (PAG) – www. Pacificassistancegroup - A team of highly trained and dedicated therapists with many years of experience treating impaired physicians, dentists, veterinarians and other health care professionals who have developed problems with alcohol, drugs, substance abuse, addiction and mental illness. PAG is able to provide a broad spectrum of services, including consultation, support

groups, comprehensive alcohol and drug monitoring services and referrals for comprehensive treatment and fitness for duty evaluations.

American Foundation for Suicide Prevention (AFSP) Physician Depression and Suicide Prevention Project. AFSP film - Struggling in Silence: Physician Depression

National Suicide Prevention Lifeline 1-800-272-TALK (8255)

http://www.black-bile.com/Whydepressedphysiciansfearfortheirlicenses.html

http://www.thehappymd.com – The "Burnout Proof" app (5 burnout basic videos, 14 prevention power tools mini trainings (none more than 9 minutes long), walking and sitting meditation, chair yoga

California Medical Association Confidential Assistance: http://www.cmanet.org/resources/confidential-assistance/

KevinMD.com - - A blog founded in 2004 by Dr. Kevin Pho, an internist, referred to as Social Media's leading physician voice. KevinMD.com shares the stories and insight of the many who intersect with our health care system, but are rarely heard from.

Over 2,000 authors contribute to KevinMD.com: front-line primary care doctors, surgeons, specialist physicians, nurses, medical students, policy experts. And of course, patients, who need the medical profession to hear their voices.

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BACLOFEN-INDUCED TOXICITY IN A PATIENT ON HEMODIALYSIS

A Case Review

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Introduction

Baclofen is a centrally acting muscle relaxant. It is a derivative of γaminobutyric acid, and works to inhibit monosynaptic and polysynaptic spinal reflexes by inhibiting GABAB receptors. It is used in spasticity, particularly in cerebral palsy, multiple sclerosis, and spinal cord lesions. Its use in people with stroke or Parkinson's disease is not recommended. (2) It is also used off label in treatment of chronic hiccups and drug abuse. Patients with decreased renal function are at risk of developing baclofen toxicity.

Objective

Be aware of Baclofen toxicity in renal insufficiency

Case presentation:

A 63-year-old Hispanic male with end-stage renal disease on hemodialysis, diabetes mellitus, with history of stroke, was admitted for osteomyelitis of the left distal toe. During his treatment, baclofen was administered orally for his chronic hiccups. Over the course of two days, it became difficult to arouse the patient. On the second day of treatment, the patient had a Glasgow Coma Scale of 8, had a mild right facial droop, delayed pupil constriction, and elevated blood pressure. Afraid that patient may have had a recurrent stroke, a complete stroke work up in the ICU was undertaken. CT showed no hemorrhage and MRI showed finding of old ischemic changes from his prior stroke without acute change. While in the ICU, the patient had a seizure episode. An electroencephalogram showed periodic bilateral epileptiform discharges. Keppra and dilantin were given to prevent further seizures. Within 24 hours, his blood pressure was brought under control, but the patient still had a Glasgow Coma Scale of 8.

Overall, a total of 4 doses of baclofen 10mg was administered during the first 36 hours of admission for the treatment of his hiccups, with the last dose occurring after his latest hemodialysis. Upon discussing further with patient's family, it was discovered that the patient had a similar reaction to baclofen in the past. Poison control was consulted, and daily hemodialysis was initiated. The

patient was given hemodialysis daily for 2 days then his original schedule for hemodialysis was resumed. The patient slowly began to become more alert and oriented as he received hemodialysis treatment and supportive care. Once the patient was stable he was transferred to a rehabilitation facility.

Conclusions:

We seriously recommend that baclofen should be used with caution in patients who are elderly, with history of brain damage, and/or with renal impairment. If baclofen is the only choice, it should be started with lower dosage and least frequency. In a study by Husseini et al., baclofen is not recommended if the estimated Glomerular Filtration Rate (eGFR) is under 30 mL/min/1.73 m^2. If the patient's eGFR is between 30 and 60 mL/min/1.73 m^2 (stage 3 CKD), it is recommended to start with low doses at longer intervals (13, 15). Hemodialysis is the mainstay treatment for baclofen-induced neurotoxicity. When a couple of sessions of hemodialysis do not provide clinical results, activated charcoal or polyethylene glycol can be used.

Discussion

We found 46 cases, including our own, that reported baclofen toxicity in patients with end stage renal disease (1, 4, 6, 7, 9, 10, 15). Lee et al. reported two patients on hemodialysis developed neurotoxicity while on baclofen (7). Hadjiyannacos et al. reported that using a small dose of 2.5mg twice daily was not associated with side effects in 2 patients on hemodialysis (4). However, increasing the dose to 5mg twice daily was associated with neurotoxicity.

Brvar et al. reported a case in which their patient was on chronic baclofen, but went into acute renal failure. The patient became comatose with a Glascow Coma Score of 5, developed hypotension, and had shallow rapid breathing. The Baclofen was discontinued when it was found to be at a toxic level (0.70mg/L). The patient woke up and was fully conscious after 4 hours of hemodialysis (6).

Himmelsbach et al. reported a case of a 36 year old woman status post kidney transplant who was given 5mg baclofen three times daily for incontinence (12). The donor kidney was rejected, and hemodialysis had to be initiated when patient developed neurotoxicity and Baclofen levels were found to be 0.57mg/L. Lois et al. reported a case of an elderly 79 year old man with ESRD who accidently took his wife's prescription of baclofen.

All these patients developed encephalopathy and recovered after hemodialysis.

Our patient also had other conditions in addition to kidney failure that may have caused him to be predisposed to baclofen-induced toxicity. To be complete, we also conducted a search to see if there were any cases that looked at baclofen-induces neurotoxicity with patients with advanced age or with brain injury.

One notable case reported by Aisen et al. that involved a patient with subclinical renal failure. She had history significant of traumatic cerebral injury (14). We found another case of a patient who had severe kidney failure, but was also was found to have an old ischemic change on brain CT (17). Our patient also had a prior stroke. Brain injury may be a risk factor in susceptibility to baclofen toxicity. Hulme et al. conducted a trail of baclofen against 12 elderly stoke patients (2). The trial was discontinued because it produced an unacceptably high level of drowsiness.

Two cases, even though the patient was not reported to have kidney failure, took notice at the monitoring plasma drug concentrations. After each hemodialysis cessation, drug concentration doubled within 10 hours (8). They speculated that this was result of the phenomenon of redistribution, where from red blood cells or peripheral tissues seep back into the plasma. Of note, this phenomenon isn't described to occur with baclofen, but it is known to happen with several drugs. Ultimately in this patient, levels were brought under control after 4 sessions of hemodialysis with concurrent polyethylene glycol and activated charcoal administration.

Baclofen is a muscle relaxant acting by inhibiting GABAB receptors. The therapeutic dosage ranges from 15-80 mg/day.

It is important to know that baclofen neurotoxicity can be also caused by other factors. There have been several cases of baclofen overdose with concurrent usage of alcohol or psychotic drugs.

Baclofen decreases excitatory neurotransmitter output and increases the effects of 1-glutamate and substance P. These neurotransmitters are involved in the pain pathway. It can also increase the release of the endogenous opioid

methionine enkephalin (1). Baclofen is partially lipid soluble, and passively crosses the central nervous system (CNS). It is found in lower concentrations in the CNS than in body serum, but it is more slowly cleared from the CNS than from the serum.

Knowing the signs and symptoms of adverse drug reactions of baclofen is important when treating patient with baclofen. Baclofen adverse drug reactions consist of CNS depression, respiratory depression, syncope, seizures, drowsiness, dizziness, weakness, confusion, hypotension, hypotonia, coma, and fatigue.

One case of baclofen overdose was reported where the patient became comatose, flaccid, and developed respiratory failure (3). A study was done that reviewed data from the Danish Poison Centre where they identified 38 cases of baclofen poisoning, and all 38 presented with symptoms of deep coma and respiratory depression (5). A case report by Chen, Bullard, Chien, and Lee showed that among a total of 9 patients, those undergoing early hemodialysis (2.7 days +/- 0.42) had a shorter recovery time than patients that received only supportive care (9 days) (9).

Brain injury may predispose patients to baclofen toxicity. History of brain injury should be taken before starting baclofen.

Renal insufficiency has an effect on the excretion of baclofen. Around 15 per cent of baclofen is metabolized into an inactive, deaminated form by the liver, and 69–85% is excreted as is in the urine (10). Glomerular filtration rate (GFR) is the primary determinant of baclofen filtration, and creatinine clearance is similar to baclofen clearance (1). When renal function is impaired, this can decrease the amount of total baclofen that is cleared in the urine, and increase the concentration of baclofen in circulation, which can lead to baclofen toxicity.

From all the cases we have reviewed, it is evident that whether the patient already has renal impairment, develops renal impairment, or takes a drug that potentiates baclofen, the patient can progress to baclofen toxicity. Also, preexisting cerebral damage, like our case, may especially develop toxic signs (12). Hemodialysis and supportive measures are the standard of care for these patients.

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GROWTH HORMONE AND ANTI-AGING

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Introduction

Since immemorial times people have wanted to live forever and to be young. Today, if we type in anti aging we get 1000's of hits in Google. There are claims to reverse aging, help with sexual potency and many other blatant claims. Some of these are medications that are supposed to increase Growth Hormone (GH) secretion. Magazines like ' Bazaar' have advertisements for compounds that taken orally can boost GH production.. There is a multimillion dollar industry for anti-aging and one of the medications is GH. The question whether GH can prevent aging seems to have already been answered

Physiology

GH is produced by the anterior pituitary gland. The hypothalamus produces growth hormone releasing hormone (GHRH). There are multiple stimuli for the production of GHRH. These may be external stimuli or from the limbic system. Other stimulants that have been well studied are exercise ,sleep and stress. Certain amino acids also have direct effects. GHRH is taken to the anterior pituitary gland. The cells in the anterior pituitary produce GH. GH is produced in bursts mainly at night, there may be a association with REM sleep. GH is taken in the blood stream to the periphery. In the liver, GH induces production of Insulin-like Growth Factor-1 (IGF-1). There are direct effects of GH in addition to effects through IGF-1. There is intranuclear binding with the GH and transcription of proteins causing multitude of effects. Besides controlling growth in children, the effects in adults are multiple. There are effects on lipids, bone and also psychosocial effects. It promotes gluconeogenesis, amino acid uptake by cells and mineralization of bone. With aging, we see that IGF-1 and GH decline. This is physiological and normal for older people and is also due to decline of GHRH..

GH Deficiency

There have been multiple studies with GH in hypopituitarism. It has been well established that GH deficiency is an entity and replacement is beneficial in multiple ways. These are improvement in psychosocial interaction, improvement in bone density, lipids and general feeling of well being among others.(6) GH replacement is monitored by levels of IGF-1.

GH therapy is injectable recombinant GH. It is given daily preferably at night. Initial dose should be small. If tolerated, it is gradually increased. Studies show that injection of GH for 2 weeks or less are not useful. It usually take 3-6 months to show the effects of GH injection.

GH in Anti-Aging Medicine

It is not clear that people who have natural decline in GH and IGF-1 with aging will benefit from giving them GH. Some of the effects of GH replacement that have been demonstrated in hypopituitarism have also been demonstrated in aging men. These effects are on bone mass and lipid as well.

Compared to young men, Rudman(4) demonstrated that giving recombinant GH to men who were healthy between 60-65 with lower IGF-1 improved muscle mass and strength. Other studies have shown the similar results. It is not clear whether long term administration of GH to elderly men may increase risk of cancer. In addition, insulin resistance may be evident. Strength training and exercise seem to be as good as GH in this group of patients.

Liu et al(3) did a systemic review on safety and efficacy of GH in the healthy elderly. Their review included many trials which were for up to 52 weeks. In this review, they looked at outcomes for body composition, strength, cardiovasular risk factors, quality of life or adverse effects. The results of this review did not see significant

difference in weight between participants receiving GH. There was a significant reduction in fat mass. Unfortunately adverse events were also present, such as soft tissue edema, carpal tunnel syndrome, arthralgia, gynecomastia. and some glucose intolerance.

There are some studies in rats which have shown that low IGF-1 may actually contribute to longevity

Clinical and Legal Issues

The FDA has approved GH for only a number of conditions : short stature in children, hypopituitarism and a few other conditions that are well defined .It is not approved for anti-aging. Distribution and prescription for off label use such as anti-aging, increasing athletic performance, is illegal. In fact physicians and other business have been prosecuted for making false claims .

Conclusions

The initial trial in 1990 by Rudman made people believe that GH could be the panacea for aging. Natural decline in GH secretion and IGF-1 are expected with age. To restore either GH and /or IGF-1 to normal levels of the young does not seem to help. Is it our natural protection against excessive growth and cancer in older people? No studies have been shown to increase cancer with increase in IGF-1. On the other hand, patients with acromegaly have increase in colon cancer. Hurel(8) discussed the effect of exercise on GH production .This may in fact be more beneficial then GH therapy, considering it has been well shown the multitude of effects of exercise on physical and mental health. Other studies have shown that exercise itself can increase GH production, Kraemer(9) showed that response of exercise in older people on GH production can vary with age.

Other treatments that has been shown to have an anti aging effect is metformin. In the last 10 years a lot of work has been done in animals with phenformin, metformin and most recently testosterone. Long term effects of metformin have been studied but are not known. neither for GH or testosterone usage in old population.

Is anti-aging the same as anti-cancer?

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P450 POLYMORPHISM

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The world of Pharmacogenetics and Pharmacodynamics has gone beyond most of our initial training. We have today a whole array of medications that are very helpful for our patients. However, on occasion, there are some patients that just do not respond like the rest. This is due primarily to the enzymatic system called the P450 system which is genetically controlled and best defined by advanced science.

In the old days we would titrate theophylline until there was nausea, vomiting and diarrhea. We would also do the same for Digoxin and/or Waban. The good old days are gone and we are much more advanced than those particular days.That being said, the P450 system is here and to be understood and to be used appropriately for our patients' benefits.The Pharmacogenetics is a major management protocol for medications. It allows us to identify drug accumulations and lack of efficacy in certain patients. Prime examples of this are the Marfan syndrome patients. These individuals frequently have pain flares and approximately 80% have some genetic deficiencies or hyperactive enzyme systems so that the P450 system needs to be taken into account and studied.5

In addition to this the sickle cell patients have P450 defects that also have a gene polymorphism in their adrenergic receptors.6 We are able to associate adverse reactions with certain medications and results in interactions. It is determined that three-quarters of the population has genetic variations that decrease or increase availability of medications due to this system. These enzymes are found in the liver and also in the intestines and are heavily relied upon for drug metabolism conversion.1 Having this valuable information with a selection of medication leads to successful patient treatments and better patient outcomes and less AEs. It also helps explain why some of our patients require very little or ultra-high opioid doses.4

Most of the P450 enzymes that we check for are CYP2D6, CYP2C19, CYP2C9, CYP384, and a new one CYP3852. These enzymes are relied upon for 70%+ for many of the routinely prescribed medications that healthcare workers use. These include but are not limited to the ARBs, beta-blockers, calcium channel-blockers, warfarin, and other central nervous system (CNS) and cardiovascular medications. These particular enzymes are also significant for our opioid or narcotic medications, NSAIDs, and most of the mood elevating medications and many of our cancer medications, i.e, tamoxifen. Most patients on Nexium® or omeprazole which is now available in over-the-counter form of 20 mg has many drug interactions. This particularly relies heavily upon the CYP2C19 enzyme metabolizer. Most of our patients are on Advil and this uses the CYP2C9 enzyme.3 Even our handy Ultram or tramadol uses the CYP2D6 enzyme for its metabolism. This P450 polymorphism has an excellent tool due to our aging population and the multiple medications that are being used. It is useful for patient's experiencing unusual or atypical side effects and those patients who do not appear to be responding to a medical regimen. Many of the medications that inhibit the aforementioned enzymes are most notable the anti-psychotic medications. These as you recall are primarily anti-choleragenic in their nature and have significant liver metabolism.

There are many companies that do genetic testing that are commercially available. Some of the better ones have been Genelex and X-Gene Diagnostics. Most of the testings are a covered benefit with the appropriate ICD 10 classification. Many of these companies have drug-drug interaction software that one can obtain through the company that they are using. It is particularly quite easy, a painless mouth swab is used, and a personal secured number given and then sent to the diagnostic center. Most insurances have been on board for these

particular tests as they see the benefit thereof. The author thinks the P450 testing is an investment in both our patients and the payers, families and we do appreciate the help of our Phar.Ds. and sage practicing physicians for advice. It is a bit more time consuming but certainly pays in the long run for the care of our patients and lessening of adverse events (AEs). We certainly improved outcomes for our patients using these systems, not withstanding less unnecessary office visits, Urgent Care visits and/or even expensive ER visits.

In interpreting these tests, many that come back are labeled abnormal metabolizers, ultra-rapid metabolizers, or slow metabolizers and one would be hoping that these labels and eponyms would be more of a uniform construct or nature. Frequently it comes back intermediate or overactive or ultra-rapid and it is a bit confusing for most of us in the field.

The most recent May issue of Practical Pain Management 2016, page 30, by the author Ramesh M. Singa, M.D., MHS, is extremely helpful, beneficial and elucidating. He speaks directly about the DNA, the cytochrome P450, analyzes the ultra-rapid metabolizers, the rapid metabolizers, and the intermediate metabolizers. A lively discussion of the various alleles, the enzymatic reaction, and the normalcy or the failure of many drugs inactivated by the CYP2C19 enzymes or the CYP2C9 enzyme ensued. He has excellent examples of a patient on a certain regimen and after genetic testing the regimen was changed around in order for an improved pain perception using the VAS scale, the visual analogue scale, and changing in his pharmacodynamic use.

The author hopes this is of benefit to those in the primary care field and those that are taking on more pain management patients. We well know that of the 125 million patients in pain there are about 6600 Board Certified Pain Management Specialists,7 primarily those in anesthesia and, specifically, fellowship trained in pain management. A few too many epidurals and a few too many neurostimulators and a few too many morphine pumps but remember where the author's roots are, the old school of primary care management.

In summary, these tests do mean something and they are of benefit and as one of my colleagues and mentors, Dr. Forest Tennant in Covina, states, "only order the test if you are willing to make changes otherwise it is useless and an expensive test."

In conclusion, may we all do things that will improve patient care and improve patient outcomes as we all live in the milieu of evidence-based medicine.

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ECMO: THE HOLY GRAIL OR THE NEW HYPE?

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Abstract

Despite the availability of extracorporeal membrane oxygenation (ECMO) for the past 4 decades, only recently there has been an unprecedented surge in its utility in treating critically ill patients with life-threatening cardiopulmonary disease. This newly found popularity is attributed to improvements in medical technology, advances in critical care and recently reported data supporting the survival benefits of this treatment. The surge in popularity of ECMO is accompanied by expansion of the application of this modality to a wider range of patients at a greater number of centers worldwide. This article reviews the principles of ECMO and its applicability within a community hospital practice setting.

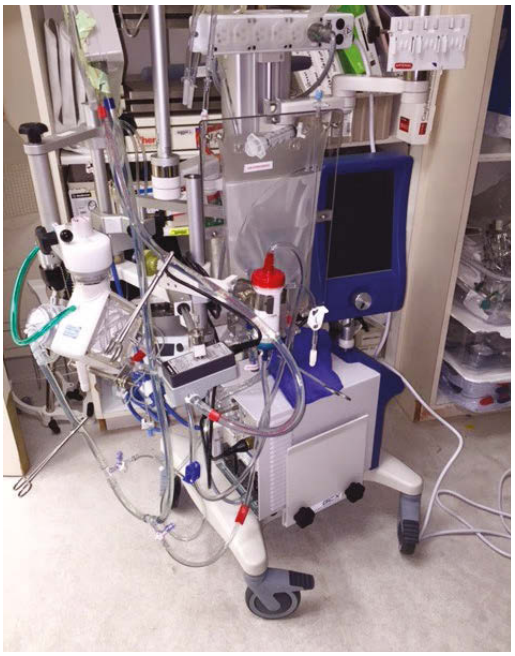
Introduction

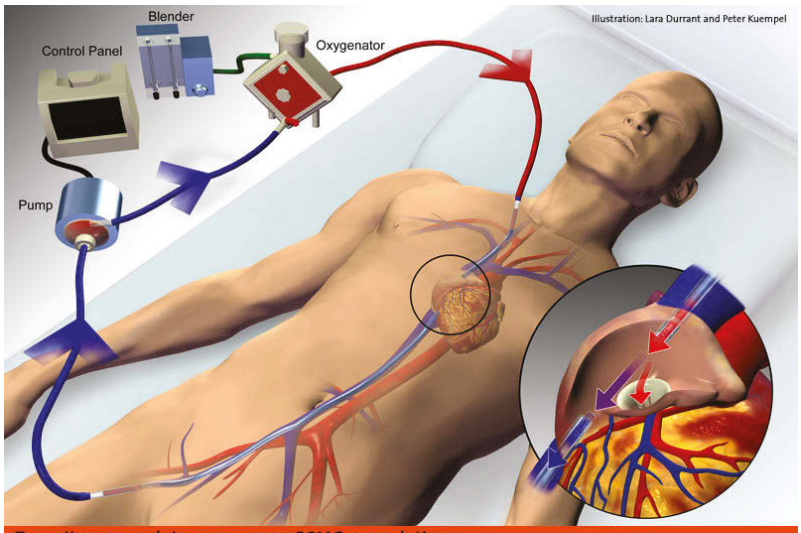
Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) refers to a cardiopulmonary support device by means of which the blood is drained from the patient's venous circulation using a large bore cannula. The blood is then delivered via heparin-coated tubing to a centrifugal pump. The pump propels the blood into a membrane oxygenator. The passage of blood through the oxygenator results in oxygenation of the blood as well as the removal of carbon dioxide. Oxygenated blood is then brought to a desired temperature via a heater/cooler component and is returned to either arterial or venous circulation of the patient.

If the patient has adequate cardiac function the blood is returned to the venous circulation at a different site from the venous drainage cannulation site. This mode of support is termed veno-venous ECMO (VV-ECMO). This type of support is strictly used for treating refractory respiratory failure. For patients with compromised cardiac function the oxygenated blood is returned into the patient's arterial circulation. This mode of support is known as veno-arterial ECMO (VA-ECMO) and it is used in patients with isolated cardiac dysfunction or in patients with combined cardiac and respiratory failure.

It is important to understand that ECMO is purely a supportive and not a disease modifying intervention in itself. It supports the patient's cardiopulmonary function until either the patient's own function recovers or until other long term treatment can be established such as, a transplanted organ or an assist device replaces it.

To date ECMO has been used worldwide to support over 70,000 patients (1). With the significant improvement in patients' outcomes, the annual usage of ECMO between 2004 and 2014 has more than tripled to a staggering number of 6962 cases worldwide in 2014 (1). As the indications for ECMO support continues to increase in literature, more questions are raised regarding what





Two-site approach to venovenous ECMO cannulation:
Cannulae are inserted in the internal jugular vein (extending to the right atrium) and the femoral vein (extending into the inferior vena cava). When the ECMO circuit is connected, venous blood is withdrawn via the femoral venous "drainage" cannula into the pump, passes through the oxygenator where gas exchange takes place, then is reinfused into the venous system via the internal jugular venous cannula. Inset: With the two-site approach, a portion of the oxygenated blood returning via the internal jugular venous cannula can be drawn directly into the femoral venous cannula without passing through the systemic circulation. Blood that is recirculated in this fashion does not contribute to systemic oxygenation.

patients should receive ECMO and which centers should provide this support. This article reviews the indications, complications, and outcomes of ECMO. In addition, we report our own experience with the first 51 cases of ECMO at San Antonio Regional Hospital, which is one of a handful of non-academic hospitals in United States that provides this highly specialized support service.

Historical Usage of ECMO

The ability to artificially oxygenate blood outside human body and then recirculate it back into the patient was brought into practice by John Gibbons. He is credited for inventing the heart-lung machine. Gibbons who as a medical student was devastated by death of a patient from pulmonary embolus began working on a way to artificially support circulation. In 1953, fifteen years after his first prototype, Dr. Gibbons performed the first open heart surgery using his heart-lung machine (2). In the following years, in addition to its use in heart surgery, modified versions of the heart-lung machine were used to prolong survival of neonates with congenital cardiac defects during the perioperative period (3, 4, 5). The first successful use of ECMO to prolong life unrelated to heart surgery was reported by Hill et al (6) in 1972. In this report VA-ECMO was used for 3 days to support a young man with post-traumatic acute respiratory distress syndrome (ARDS) following a motorcycle accident. Shortly after, multiple case reports and case series were published reporting various degrees of success with ECMO in supporting both neonatal and adult population. To build on the initial success of a promising therapy, the National Institute of Health (NIH) initiated a randomized controlled trial of VA-ECMO versus conventional therapy for treatment of ARDS (7). The results of this trial showed 90% mortality for both the ECMO and the conventional treatment arms. Despite the subsequent reduced enthusiasm, specialized centers in Europe and United States continued to work on modifying the technique as well as the equipment of ECMO. A decade and half later in 1994, Morris et al. published a second randomized controlled trial comparing ECMO to conventional mechanical ventilation for treatment of ARDS (8). This trial showed 33% survival in the ECMO group versus 42% in mechanical ventilation group. More recently, a prospective randomized study,

Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure (CESAR) trial (9), however showed a significantly higher 6 months survival with ECMO than with conventional treatment (63% v 47%; relative risk # 0.69; 95% confidence interval [CI], 0.05-0.97; p # 0.03). The discrepancy between the outcomes of these 3 randomized trials is partly explained by the improvements in the ECMO technology over the past decade. Further more, in the two earlier trials, in contrast to CESAR, the current ventilatory strategies for treatment of ARDS such as lung rest and permissive hypercapnia were not used. Since CESAR, there has been multiple non-randomized series reporting survival of up to 76% with ECMO in treating ARDS patients (10). More significantly, publication of CESAR has resulted in a surge in usage of ECMO as well as increase in the number of centers providing this intervention (Figure 1).

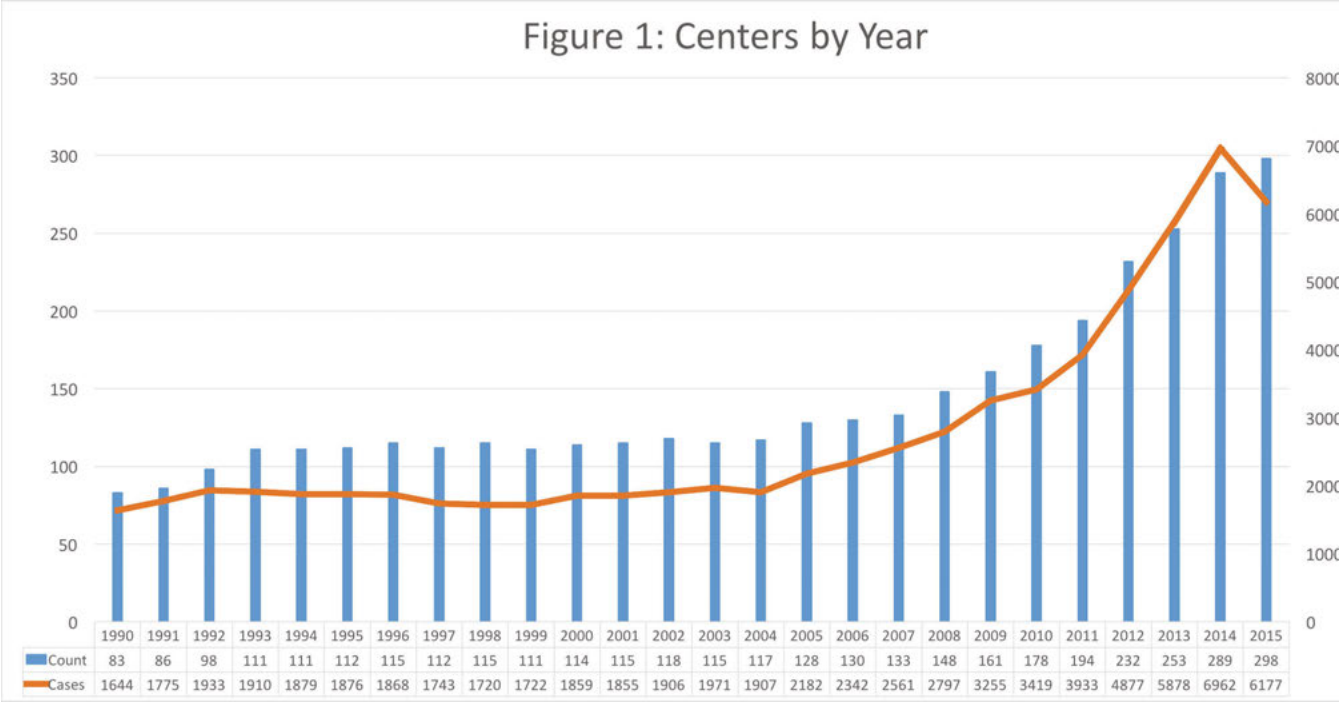


Figure 1: Centers by Year from ELSO 2016 study (1)

Indications for ECMO

It is important that right at the onset of evaluating a patient for ECMO the realistic goal of the intervention is determined and communicated to patient's family members.

ECMO is a supportive measure allowing for circulation of oxygenated blood in the setting of a life-limiting cardiopulmonary failure. This supportive measure is applied as a bridge to decision, a bridge to organ recovery, or a bridge to organ replacement therapy (e.g. assist device or transplant). If ECMO is deemed unlikely to result in meaningful patient recovery then this intervention should not be offered, or if the patient is already supported on ECMO, then consideration should be given to withdrawal of the ECMO support. The list of conditions that likely will not result in a survival benefit for a patient even with ECMO are listed in Table 1.

Table 1- ECMO Contraindications
Unrecoverable heart or lung failure and not a candidate for organ replacement therapy
Severe brain injury
Disseminated malignancy
Unwitnessed or prolonged CPR with inadequate tissue perfusion
End-stage organ disease such as liver failure, emphysema
Aortic insufficiency
Aortic dissection

Table 2- ECMO Indications	
Conditions causing cardiac failure	**Conditions causing respiratory failure**
Acute coronary syndrome	Acute respiratory distress syndrome
Pulmonary embolism	Pulmonary contusion
Cardiomyopathy	Airway obstruction
Post-cardiotomy shock	Status asthmaticus
Primary graft failure post heart transplant	Primary graft failure post lung transplant
Intractable arrhythmia	COPD exacerbation
Hypothermia	Anaphylaxis

ECMO in general is indicated in any condition resulting in life-threatening respiratory failure, cardiac failure or both as illustrated in Table 2.

Outcomes

Table 3 summarizes the most recent pooled international outcome of centers enrolled in Extracorporeal Life Support Organization (ELSO).

As summarized in Table 3, neonatal and pediatric patients tend to have much more favorable outcomes than adults (11). Across all age groups ECLS for respiratory failure is associated with the highest likelihood of survival. In contrast, extracorporeal pulmonary resuscitation (ECPR), which refers to initiation of ECMO at the time of cardiopulmonary resuscitation (CPR), has the least likelihood of survival. It is expected with the continued improvements in outcome of patients receiving ventricular assist devices (VADs) and artificial hearts, the survival of patients recovering from cardiac failure to improve in future.

Reports from various individual centers in general have shown similar outcomes to the International Registry for ECLS. As previously mentioned, to date there have been only two randomized control trials investigating outcomes of ECMO in respiratory failure. No randomized trial has been published to study the outcome of ECMO in cardiac or ECPR patients.

Over the past two decades there has been a significant improvement in the survival of the adults treated with ECMO. This trend in better survival has been attributed to advances in critical care management of the ECMO patients, as well as the improvements in perfusion technology used in ECMO circuits. The advances in perfusion technology include the use of biocoating the pump tubing, more efficient centrifugal pumps, and better oxygenators. As seen in Table 3 a significant percentage of patients despite surviving ECLS (column 3) proceed to expire due to failure of other organ systems. As the use of ECMO continues to sharply grow in upcoming years, further research needs to be directed towards improving the survival to discharge (column 4) after a successful ECLS run. In particular, ECMO survival is expected to improve as we continue to learn more about improving patient selection, protecting organs while on ECMO support and the reduction of deleterious effects of systemic inflammatory response syndrome.

ECMO in Non-Academic Hospitals

Despite the recent worldwide surge in number of centers offering ECMO to critically ill patients, the use of this technology still remains limited to academic/ tertiary care facilities. This is predominantly due to the cost and expertise required to initiate a successful ECMO program. Starting in 2011 we began to develop an adult ECMO program at San Antonio Regional Hospital in Upland, California. San Antonio Regional Hospital is a non-academic 363-bed acute care located in the Inland Empire region of Southern California. The current population of the Inland Empire is estimated to be 4 million. The newly developed ECMO service at San Antonio Regional Hospital remains the only adult program serving the Inland Empire. The impetus behind initiating an ECMO program at San Antonio Regional Hospital was the fact that critically ill patients frequently present to both tertiary care as well as community based hospitals. The subgroup of patients who benefit from lifesaving ECMO support are often too unstable to be transferred to the nearest tertiary care center. Since its start in 2011, the number of patients supported on ECMO has dramatically increased. Table 4 summarizes the demographics as well as the outcomes of our first 51 patients treated with ECMO at our community-based hospital:

Table 3 Overall Outcomes ELSO

	Total Patients	Survived ECLS		Survived to DC or Transfer	
Neonatal					
Respiratory	28,723	24,155	84%	21,274	74%
Cardiac	6,269	3,885	62%	2,599	41%
ECPR	1,254	806	64%	514	41%
Pediatric					
Respiratory	7,210	4,787	66%	4,155	58%
Cardiac	8,021	5,341	67%	4,067	51%
ECPR	2,788	1,532	55%	1,144	41%
Adult					
Respiratory	9,102	5,989	66%	5,254	58%
Cardiac	7,850	4,394	56%	3,233	41%
ECPR	2,379	948	40%	707	30%
Total	73,596	51,837	70%	42,947	58%

Table 4- Outcomes at San Antonio Regional Hospital

	Total	**Survived to transfer or discharge**	
Respiratory	17	11	65%
Cardiac	20	11	55%
ECPR	14	6	43%
Total	51		

Age: 24-73 (Mean 56), Male: 34 patients, Female: 17 patients

Amongst our notable survivors there is a 54-year-old male who received over 90 minutes of CPR and currently is 3 years post discharge without any neurological deficits. In 2014, during the N1H1 flu-season two 23-week pregnant females were presented to San Antonio Regional Hospital with ARDS. After failing conventional ventilator support both patients were successfully treated with VV-ECMO for approximately 14 days. They successfully went on to give birth to their children without any complications.

Summary

There has been an increase in utilization of ECMO in management of critically ill patients with cardiopulmonary failure. This resurgence can be explained by the newly published data showing benefits of ECMO along with recent technological advances in extracorporeal support. ECMO management is labor intensive and requires collaboration amongst multiple specialists including cardiothoracic surgeons, cardiologists, intensivists along with dedicated team of nurses and perfusionists. As a result, until recently ECMO was solely being used at tertiary care/academic centers.

However, given the clear benefits that the recent research has shown, ECMO is increasingly being used at community hospitals. We are very fortunate to have the clinical expertise and dedicated staff that have made it possible to bring this technology to Inland Empire region. Our outcomes at San Antonio Regional Hospital are equivalent to the national outcome data. As we gain more experience, our goal is to offer this modality for Inland Empire region and serve as a flagship hospital for extremely critically ill patients.

Acknowledgements

We like to thank Mr. Randy Miller and Mr. Tim Baker for all their hard work and dedication as our lead perfusionists to help devise and support the ECMO program at San Antonio Regional Hospital.

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MEDICAL ETHICS AND CALIFORNIA'S END-OF-LIFE OPTION ACT:
An Overview

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On October 5, 2015, Governor Brown signed into law the End of Life Option Act (EOLOA). The law went into effect on June 9, 2016. This law legalizes "physician-aid-in-dying" (sometimes called "physician-assisted suicide"), which allows a competent adult resident of California with a terminal diagnosis confirmed by two physicians to initiate a process for obtaining a prescription for drugs that can be self-administered to end the person's life. Throughout this article I will refer to this as "physician-assisted death." The purpose of this article is to provide some background and context in which to understand this new law, to see how it impacts the rights of patients and physicians, and to understand the challenges physicians and hospitals may face in its implementation. I will share data suggesting what type of patient is most likely to request assisted death, and in addition what we know to this point about how healthcare providers around the state are implementing the law. Policies on EOLOA at some hospitals in the Pomona region will be explained and frequently asked questions will be addressed.

1. Background

How did we get here? Some readers may be unaware that both the law on and attitudes regarding physician-assisted death have been changing sharply over the past few years. But first, we need to make an important clarification: physician-assisted death is not to be confused with euthanasia, which is not legally approved anywhere in the United States. According to the American Medical Association, euthanasia is defined as: "the administration of a lethal agent by another person to a patient for the purpose of relieving the patient's intolerable and incurable suffering" [1]. Physician-assisted death, by contrast, must be self-administered by a patient capable, mentally and physically, of doing so. Thus the death occurs as a direct result of the patient's actions, not those of the attending physician.

a. Changes in the Law

The legal landscape of physician-assisted death, both in the U.S. and elsewhere, is changing. While as recently as the mid-1990s, no American jurisdictions allowed physician-assisted death by law, six (as of the time of this writing) now do so [2]. Four of these states (California, Oregon, Washington, and Vermont) have legal protocols in place specifying criteria and procedures for obtaining access to physician-assisted death. Other states have considered such legislation and support nationwide appears to be growing. [3] [4].

Changing attitudes are also apparent in public opinion surveys. Three polling organizations recently surveyed Americans on the subject of physician-assisted death and reported similar results: 60-70% of Americans now say a person suffering great pain with no real hope of improvement should have a right to end his or her life [5] [6] [7].

Majorities supporting physician-assisted death (though by smaller percentages) were reported by two other polls [8]. A recently published study found that Americans' acceptance of physician-assisted death rose from 37% in 1947 to 61% in 1999 [9]. Increasing legislative and popular support for physician-assisted death is evident as well in other countries, including Scotland [10], France [11], Canada [12], and other European nations [13] [14]. In early 2015 the Supreme Court of Canada invalidated laws in the country banning assisted death [15].

b. Changes in Institutional Policy

Not surprisingly shifting legal conditions in respect of physician-assisted death are bringing with them changes in institutional policy. While many hospitals previously condemned assisted death [16], hospitals in states allowing it are beginning to formulate protocols and plans in anticipation of patient requests for assistance in dying. Data available from Oregon and Washington—states with the longest record of implementation with respect to physician-assisted death—shows that some hospitals and medical centers are supporting access to physician-assisted death, while others (notably, Catholic facilities) are not [17] [18] [19]. Physicians in Seattle and in Portland have described the implementation of policies for assisted death, as have several hospices programs in those regions [20] [21] [22]. Hospitals in countries that allow assisted death have done the same [23].

c. Changes in Professional Standards of Practice

The clear majority of American medical organizations and societies of healthcare professionals are on record as being opposed to the practice of physician-assisted death, though this stance is by no means unanimous; and some such bodies have explicitly refused to take a position on the allowability of physician-assisted death. The most prominent organizations, such as the American Medical Association, the College of Physicians, and the American Nurses Association have voiced long-standing opposition to assisted death [24]. Other associations including the American Society of Pain Management Nursing, the American Medical Directors Association, and the American College of Medical Quality join them [25]. But the American Public Health Association supports assisted death, and while the Hospice and Palliative Nurses Association opposes the its legalization, the organization nonetheless counsels nurses working in states where physician-assisted death is legal to "guard against communicating a negative judgment" on patients who elect to pursue it [27].

Perhaps most notable is the growing number of societies adopting what amounts to a neutral stance on the moral status of physician-assisted death. Emblematic of this stand is the position staked out by the American Academy of Hospice and Palliative Medicine (AAHPM). The AAHPM "takes a position of 'studied neutrality' on the subject of whether physician-assisted death should be legally regulated or prohibited," and cautions its physician members to "carefully scrutinize" requests for assisted death and proceed with "great caution before instituting physician-assisted death…" [28]. The American Academy of Physician Assistants argues that though "liberalization of assisted suicide could have unintended consequences, so too could absolute restriction on assisted suicide" [29]. The American Pharmacists Association does not endorse particular moral stance on the issue of physician-assisted death, nor does the American Society of Health-System Pharmacists [30] [31]. The National League for Nursing adheres to the "belief that a single position on the part of this organization would not be helpful at this time" [32].

Among hospice nurses and social workers surveyed in Oregon, ninety-five percent indicated that their hospice agency should either support a patient's choice for physician-assisted death, or at least remain neutral [33]. Some prominent ethicists, such as Timothy Quill, encourage the adoption of such a neutral position [34]. State medical societies in jurisdictions sanctioning physician-assisted death by law appear as well to be opting for this neutral view, neither opposing nor supporting physician-assisted death [35] [36] [37]. In May 2015, the California Medical Association dropped its opposition to physician-assisted death in the face of widespread support for the End-of-Life Option Act. The CMA is the largest statewide medical association to adopt a position of neutrality [38].

2. What Type of Patient is Likely to Request Assisted-Death?

The best data we have to date on how the new California law might work comes from the state of Oregon, which has had an almost identical law since 1997. A brief review of this data may give us some idea of the kinds of California residents who make come to us asking about assisted death.

In 2015, 218 prescriptions were written for patients in Oregon under the provisions of their law; 132 of the prescriptions were used. Of the 132 decedents, 78% were age 65 or older; the median age was 72; 95% of decedents were white and well-educated (47% had a college degree). 42.4% of the patients were male; 57.6% were female. 72% of the decedents were diagnosed with terminal cancer and 6.8% with ALS, with the remainder suffering from a variety of terminal conditions. The overwhelming majority (89.5%) died at home; 92% were enrolled in hospice care either at time prescription was written or at time of death; 99.2% had some form of health insurance [39]. The drug typically used in Oregon over the years has been a high-dose barbiturate along with an antiemetic: 9 grams of Seconal (secobarbital) capsules is a typical prescription [40].

The three most frequently cited end-of-life concerns among those who have sought physician-assisted death in Oregon have been consistent over the years: Decreasing ability to participate in activities that make life enjoyable (96.2% in 2015), loss of autonomy (91.4%), and loss of personal dignity (75.4%). Of the 218 patients who obtained a prescription under the law in Oregon in 2015, 3.8% were referred for psychological/psychiatric counseling. Approximately 0.5 %, or one in 200, of physicians licensed to practice in Oregon have agreed to write prescriptions under the Oregon law. [41].

3. Main Provisions of the California Law

Under California's new End-of-life Option act, a patient seeking to die must be an adult resident of California, and two physicians must confirm that the individual has capacity to make an informed decision and has a terminal condition. The patient must make two voluntary oral requests 15 days apart, and a written request witnessed by two people, neither of whom is a treating physician. The attending physician must refer the patient to a mental health professional if there are indications of a diagnosable mental disorder. The attending physician must also counsel the patient on alternative forms of end-of-life care and determine the patient is not subject to coercion or undue influence by talking with the patient outside the presence of any other persons. A patient must be told she can change her mind, and also that she may obtain drugs but choose not to use them. Patients should be advised not to ingest drugs in a public place [42].

Under the EOLOA, the attending physician must document all conversations and findings pertaining to activities authorized by the Act and report the information to the State Department of Public Health within 30 days of writing a prescription. Physicians, pharmacists, and others who do assist a patient pursuant to the Act are not subject to civil or criminal liability, or to disciplinary action [42].

From an ethical point of view, the most important fact to know about this new law is that participation in activities authorized by it are completely voluntary. No physician or other health care provider is required participate, make a referral, or even provide information about the law. A hospital may prohibit the exercise of activities relating to the EOLOA on its premises or by its staff, employees, or contractors, though it must give notice of its intention to do so; however, the hospital cannot prohibit a medical staff member from making a referral or providing information about the law if he/she chooses to do so. Finally, a hospital cannot prohibit a medical staff member or employee who, in off hours, and not on hospital premises or working within the scope of his or her employment, chooses to participate from doing so [42].

4. Implementation of the Law

Implementation of EOLOA is just beginning. We have some information about who is and who isn't participating, but much remains unclear at this time.

We have no solid data as of this writing on which hospitals and providers intend to participate; neither the state Department of Public Health nor the CMA are collecting comprehensive statewide statistics; much of the data currently available comes from organizations that supported the new law, such as Compassion & Choices. According to this information, many faith-based hospital organizations (e.g., those affiliated with Adventist Health and Dignity Health) are choosing to prohibit medical staff from any participation; this is also true for the VHA, because federal funding cannot be used to facilitate assisted death. Other regional and state facilities have announced that they will participate. These include Harbor-UCLA; UCSF and other University of California hospitals, Cedars-Sinai, and LAC +USC. Sutter Health and Kaiser Permanente are also apparently permitting staff to participate [43].

Many hospitals in the greater Pomona region are allowing individual staff members to participate or not as they choose, but are electing not to facilitate assisted death or allow the drugs to be dispensed or ingested in any inpatient areas. This is the policy of both Pomona Valley Hospital Medical Center and San Antonio Regional Hospital. At PVHMC, patients and medical staff may make their own personal choices regarding assisted death; patients who request it will be provided with general information on the law. Medical staff members may, if they choose, provide patients with a referral for assistance in obtaining assisted death; however, staff members may not administer or assist with administering drugs to end life on hospital premises, and the PVHMC pharmacy will not honor orders for medications as defined in the law. One significant reason for these limitations points to the waiting periods involved and the rights of hospital associates to "opt out."

5. Frequently Asked Questions

a. What to List as Cause of Death?

When a patient dies from ingesting drugs procured under the EOLOA, what is the attending physician to list as the cause of death? Though the law itself stipulates that "actions taken in accordance with [this Act] shall not, for any purpose, constitute suicide..." it is silent on what can be listed as the cause. Fortunately, there is now guidance from the state Department of Public Health on this question, issued in June of this year. According to the CDPH "certifiers should not report the cause of death as 'pursuant to End of Life Option Act'..." instead the CDPH "recommends that [certifiers] report the underlying terminal disease as the cause of death" [44].

b. Will Insurance Cover the Costs?

The law does not require health plans to cover the costs of services provided or medications prescribed under the law. It is also clear that Medicare will not cover any costs associated with EOLOA, since (again) federal funding may not be used for that purpose. This may be significant, given that in recent years in Oregon nearly 80% of patients who obtained prescriptions for life-ending medication were over 65 or older. Medi-Cal, however, will cover costs [45].

c. Where Can I Find the Required Forms?

All of the relevant forms pertaining to the End-of-Life Option Act and information on how to fill them out are available through the state Department of Public Health [46].

d. Where Can I Find Clinical Guidance on Assessing Capacity, Prescribing, etc.?

A recent article from the Journal of Palliative Medicine has some useful guidance [47].

e. To Whom Can I Refer Patients to Obtain Assisted Death If I am Not Participating?

Currently there is no clear information on how to access a network for referrals. The best option is to refer patients generally to Compassion & Choices at http://endoflifeoption.org/ They also have a toll-free number: 1-800-247-742.

6. Conclusion

Asking a physician to assist in ending his or her patient's life has been controversial going back to ancient times and the writings of Hippocrates of Cos. That debate is still with us, and while some of the questions surrounding the implementation of California's End-of-Life Option Act are being addressed, only time will tell how it will be received and used.

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SURGICAL TREATMENT OPTIONS FOR PATIENTS WITH EPILEPSY

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Introduction

To discuss the history of Epilepsy Surgery, one must include the work of Dr. Wilder Graves Penfield, one of the most influential members of the field. He had many contributions to the field of medicine including development of the Penfield instruments used by neurosurgeons daily for a variety of procedures (Fig 1), founding the Montreal Neurological Institute at McGill University, and mapping the motor and sensory homunculus in humans.1

In terms of epilepsy surgery though, his greatest accomplishment was improving our understanding of the ictal onset zone using awake intracranial stimulation. Dr Penfield and his epileptologist colleague, Dr Herbert Jasper, conducted several experiments on awake patients undergoing craniotomy to better understand the ictal onset zone. They would take patients with epilepsy and a brain lesion (eg tumor, stroke, trauma, etc) and use an intracranial stimulator to stimulate the patients in surgery. They found that when they stimulated the lesion, patients rarely had seizures. It was only when they stimulated the brain tissue surrounding the lesion that they were able to elicit seizures in the patients (Fig 2). They also found that the lesion and the ictal onset zone must both be removed to render the patient free of seizures.1

The pioneering work of Dr. Penfield and Jasper have given us an improved understanding of epilepsy and the surgical treatment of epilepsy. Since that time, our understanding of epilepsy has grown significantly and we have new zones that have been described that are related to the ictal onset zone (Figure 3).

Decision Making Process

Patients are only considered to be candidates for epilepsy surgery if they have failed at least two seizure medications. An excellent randomized controlled trial of medication compared with temporal lobectomy was performed by Wiebe et al in 2001 which showed that

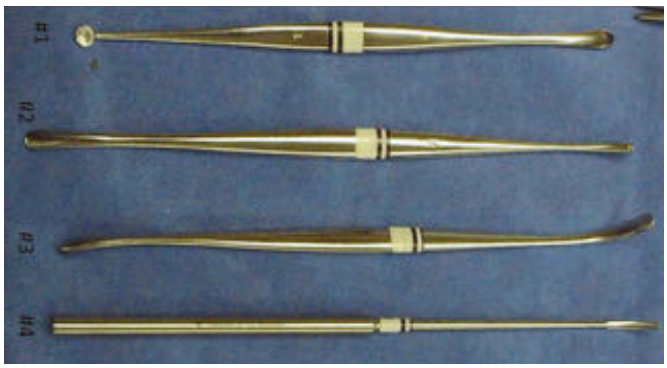

Figure 1: Penfield Instrument set used by neurosurgeons for a variety of procedures

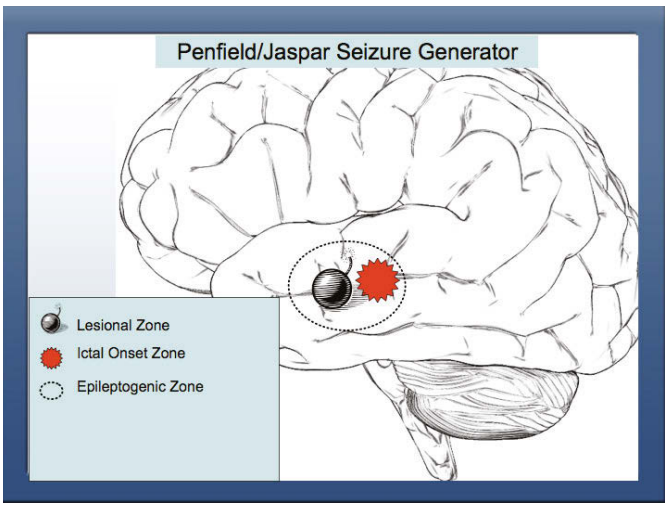

Figure 2: Experiments performed by Penfield demonstrate lesional zone and ictal onset zone must both be resected for seizure freedom.

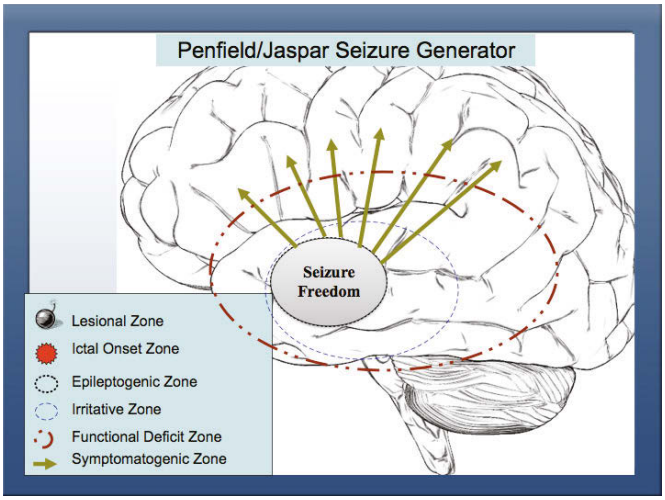

Figure 3: Other zones of the brain related to ictal onset zone. The Irritative zone, which is the area of the brain which generates interictal spiking which can be seen on a scalp EEG, the functional deficit zone is the region of the brain that is functionally abnormal during the interictal period. This is best seen on a PET scan. Finally, the symptomatogenic zone is the area of cortex which produces initial symptoms during a seizure.

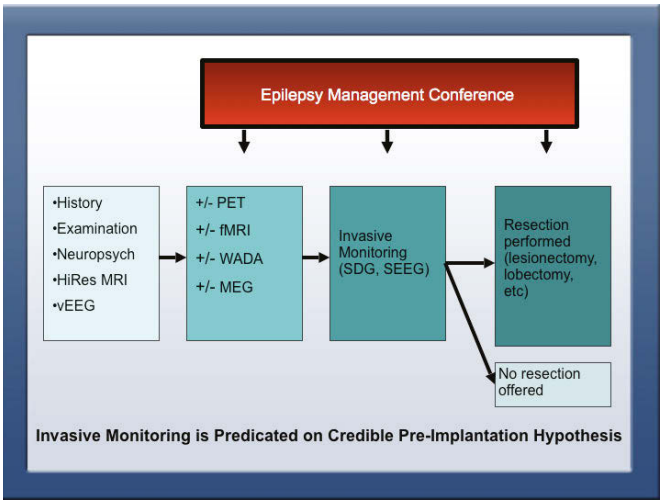

Figure 4: Decision making for epilepsy surgery. Note that invasive monitoring is not always required and patients may go straight to therapeutic surgery if all studies are concordant.

surgery is superior to prolonged medication in patients with medically refractory epilepsy.2 Unfortunately, the use of lobectomy is underutilized for the treatment of patients with medically refractory focal epilepsy.3

For epilepsy surgical work-up, patients should be evaluated at a Level 4 Epilepsy center as accredited by the National Association of Epilepsy Centers (NAEC). To be deemed a Level 4 center by NAEC, "serve as regional or national referral facilities for intractable epilepsy patients. These centers should provide the more complex forms of intensive neurodiagnostic monitoring, as well as more extensive medical, neuropsychological, and psychosocial treatment. Fourth-level centers also offer a complete evaluation for epilepsy surgery, including intracranial electrodes, and provide a broad range of surgical procedures for epilepsy."4

All patients that discussed by a multidisciplinary panel of neurologists, neurosurgeons, neuropsychologists, and neuroradiologists – The Epilepsy Management Team - and only then, a final decision is made regarding whether surgery should be offered, and what type of surgery should be performed. In this way, a unique clinical hypothesis is created for each patient as to the location of their epileptogenic zone and a consensus is formed between all specialties, which allows for the patient to have the best possible chance for seizure freedom.

All patients that present to the epileptologist for surgical planning first undergo a detailed history and physical examination, neuropsychological testing, high-resolution MRI and video-EEG. They are discussed in the Epilepsy Management Conference at which point the group may recommend further testing such as PET scans, fMRI, WADA tests amongst others. If the non-invasive tests do not correlate, the patient may require further diagnostic procedures to better understand where the seizures arise at which point they patients undergo invasive intracranial monitoring with either subdural grids or stereoelectroencephalography (sEEG) depth electrode implantations. Based upon the outcomes of these procedures, the patient may go on to have a therapeutic surgery to treat the ictal onset zone. This surgery may be a resection, laser ablation, or neurostimulator implantation amongst others. Of course, not all patients require invasive electrode implantation and so if all noninvasive techniques suggest a single location for the ictal onset zone, patients may go directly to therapeutic surgery to treat the cause of their seizures (Fig 4).

Invasive Electrode Options

The specific intracranial electrode options available to patients include subdural grids and sEEG as stated above. After patients have electrodes implanted in surgery, they are admitted to the epilepsy monitoring unit where they are monitored for seizures. Once an adequate number of seizures is captured (usually within one week), the patient is brought back to the operating room for

removal of the electrodes and treatment of the ictal onset zone. While a detailed review of these options is outside the scope of this paper, it is important to note that the decision to implant SDG or SEEG is based upon the patient's clinical presentation and the preimplantation hypothesis of the location of EZ.

In broad terms, subdural grid electrode implantation is best utilized if the hypothesis for the seizure onset zone is located near functional regions of the brain such as the motor area of the language areas. In these patients, subdural grids implantation allows for precise mapping of the ictal onset zone as well as the functional cortex and how the two regions are related. Once the ictal onset zone is localized, the epileptologist performs functional mapping which entails introducing a low level of electrical current into the various electrodes and assessing for any functional impairment that this creates. For instance, if a patient develops difficulty with speech during electrical stimulation of an electrode, the underlying brain tissue is considered to be part of the speech area and is mapped accordingly. During surgery, these areas should not be resected to avoid postoperative aphasia. The main drawback to this type of surgery is that the surgery requires a large craniotomy and implantation of grids on the brain which has the risk for infection and blood clot formation. Fortunately, the risks of these complications are very low when performed at centers with high volume and experience.5-8

Stereoelectroencephalography (sEEG) is a minimally invasive procedure that implants several depth electrodes through small openings in the scalp. The accuracy and precision of this procedure have been improved with the use of a robot and other stereotactic navigation devices.9-11 This procedure is excellent when sampling several lobes of the brain or when sampling both hemispheres of the brain. As the procedure needs only several small incisions in the scalp, patients do not require large craniotomy or large incisions on the scalp. Once the ictal onset zone is localized, patients have the electrodes removed and then usually undergo therapeutic surgery at a later time. This procedure is not as precise at mapping functional locations but is an excellent surgery when a large network is suspected or when deeper structures are believed to be involved.

Therapeutic Options

Once the ictal onset zone is localized, there are three possibilities for treatment: 1) the patient has multifocal epilepsy or non-localizable epilepsy in which case Vagus nerve stimulation may be offered as a palliative treatment options; 2) the patient has a single focus that can be resected without causing a long-term deficit or 3) the patient has a single focus that is close to or intermixed with functional tissue or two distinct ictal onset zones that cannot both be resected in which case neurostimulator devices may be beneficial (eg. Responsive Neurostimulation).

Surgical treatment options depend upon all the patient's clinical presentation and any data collected through invasive and non-invasive techniques. In terms of resective procedures, temporal lobectomy has an excellent seizure free rate which is quoted in the literature between 60-80%, but other resective procedures are also available including lobectomy and lesionectomy as well as hemispherectomy.2,5,9-11 Responsive Neurostimulation has recently been FDA approved for treatment of patients with ictal onset in areas of the brain that might result in functional deficit or in bitemporal seizure onset. This device is implanted around the ictal onset zone and constantly measures EEG readings looking for seizures. The device detects and responds to seizures directly and can shorten the duration of the seizure or abort the seizure before it propagates. The device has been used for a variety of patients with medically refractory epilepsy in functional regions with good success rates.12

Conclusions

Epilepsy surgery offers us the chance to treat and possibly cure patients with a devastating disease process when they fail medications. Epilepsy surgery has offered us a glimpse of the underlying functions of the brain and its pathologic states and utilizes state-of-the-art devices and techniques to treat patients. There are two broad classes of surgery which include diagnostic procedures and therapeutic surgery. New devices are available that can treat some of the most challenging forms of epilepsy and the field continues to grow.

When caring for patients with epilepsy, it is important to consider epilepsy surgery as an integral part of the armamentarium to treat these patients and not as a last resort. Patients should be referred to a Level 4 Epilepsy Center where all the newest clinical trials and surgical procedures are being performed and patients can receive the best chance to become seizure free.

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COMMUNITY PREPAREDNESS FOR INFECTIOUS DISEASES

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When Ebola struck West Africa in 2014, it caught local communities, governments and NGOs off guard, and the rapid spread and severity of the epidemic surprised even the global health community. Local people were mystified by the rapid mortality, the mode of transmission and the apparent vulnerability of anyone who came near an Ebola victim — alive or dead. Superstitions and cultural traditions, which naturally fill an information void, led to behaviors that made matters worse and stirred great fear, contributing to civil unrest and alienation among neighbors, just when cooperation was needed to stem the spread of this virulent disease (14, 15, 16).

It took several months for international health experts to set up treatment facilities, to establish suitable procedures for dealing with the sick and the dead and to address the wild misperceptions that had matured during the early days of the onslaught. Once it became clear that something tragic was unfolding in Guinea and soon in Sierra Leone and Liberia, word of the Ebola outbreak spread rapidly across Africa, then beyond the continent; the waves of alarming information perpetuated concerns, often inspired by myth, far beyond the infected region.

For more than a year Ebola cut a swath through the affected region (29,000 cases with 11,000 deaths [2]), but at long last, the outbreak was contained, and while the impact devastated local populations, contamination remained reasonably confined to a handful of countries on the western edge of a very large and vulnerable continent (9, 10). In the face of the Ebola episode, questions naturally arise about whether the disease would have taken such a hold if communities had been prepared for the outbreak. Would general knowledge about Ebola — including the nature of the disease, the mode of transmission, effective precautions against infection — have checked its spread? We can never know for sure, of course, but we do know that in the face of an impending infectious disease, populations can take measures that reduce the odds of spreading an infection and that increase the outcomes of successful responses, contributing to a more rapid resolution. For this to happen, people must be educated about the disease and about measures they can take to curb its spread.

Successfully addressing Ebola, like so many other infectious diseases, depends on a coordinated effort within a community (8, 12). That may seem obvious, but in too many instances it's ignored. To reduce the spread of many infections, governments can marshal resources and provide security; NGOs can summon experts who arrive with supplies with which to slow transmission and treat the ill; community leaders and businesses can plead for calm and a rational response; and the media can blanket the population with accurate information and guidance. Of course, all this points to the importance of teaching the population about the illness, activating people to take proper prevention measures and to recognize signs and symptoms that signal the need for early medical attention.

WiRED has dedicated this community preparedness project to the memory of Ambassador J. Christopher Stevens. Amb. Stevens represented the United States in Libya, where he was killed in 2012. As a Peace Corps Volunteer in Morocco in the 1980s and Ambassador to Libya, Amb. Stevens had a deep regard for small communities and for the health of people in these remote places. He worked with community leaders to foster improved medical conditions and to ease the burdens of poverty faced by populations often forgotten by governments and other institutions. Our community preparedness project offers a tool for low-resource populations to make ready for an epidemic. We believe this effort supports the work begun by Amb. Chris Stevens.

Here's the challenge we see: In low-resource regions, where poverty and lack of resources render a population especially vulnerable, how do we stimulate concern for an impending infectious disease? How do we coordinate the efforts of key community leaders and sync them with each other and with the general public in a concerted effort to head off a punishing outbreak? How do we teach people about the features of a disease that they can use to shore up their defenses?

Community education for infectious diseases

In the spring of 2014, months before the United Nations called the Ebola outbreak an international health emergency (9), WiRED International had created and distributed four educational modules to train the general public and health workers about characteristics of the disease and about donning personal protective equipment and using proper burial techniques and sanitation measures. At that early time in the epidemic, little more than posters were available to explain Ebola to the general public and not much detailed and authoritative material was on hand, even for health and medical professionals, including hospital staff and community health workers. WiRED's computer-based, training material, available in English and French, was widely distributed on the Internet and by NGOs working in the area.

Dogged efforts by local workers and a number of organizations, such as the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), Caritas Internationalis and Oxfam brought the Ebola epidemic to a gradual, although not complete resolution, leaving West Africa to clean up after a deadly bout with an unforgiving disease. Evaluations of global response to the Ebola epidemic started soon after the interventions began and continue to this day.

We at WiRED extended our own analyses of this Ebola episode to a broader range of infectious diseases. While Ebola was particularly frightening, given the virulent nature of the virus, the speed with which it kills and the horrors it wreaks on the human body, it is only one of many infectious agents that ravage human populations. Thus, looking more broadly, we consider two elements in a single frame: (1) the educational tools available to affected communities and (2) the communities' coordinated response to prepare for and to deal with a large-scale infectious disease. In other words, what can we do to teach people about an infection potentially coming their way and how do we help the community join hands in a concerted effort to combat it.

With financial support from Medtronic Philanthropy, WiRED's team set out to design a training solution that would create a set of modules that identified six key groups critical in most communities, five modes of transmission and a starting collection of 40 disease-specific modules that discuss in detail a description of each disease, its signs and symptoms, diagnosis, treatment and prevention. We will discuss this in the section below.

Six key community groups

In response to the Ebola epidemic in West Africa, Center for Disease Control focused on a handful of groups whose role in the community was key to addressing the epidemic (1, 6, 8). We used that analysis along with other discussions about community preparation (2, 7, 4, 3) to identify six key groups for training programs in this project:

1. Health workers
2. Local governments
3. Community leaders (non-governmental)
4. The media
5. Transportation resources
6. The general public

We developed a stratified training program, where we direct specific instructions and discussions to community members who categorize themselves into one of these six groups.

Modes of transmission

WiRED adapted the five modes of transmission selected for this project from CDC's position paper on the chain of infection (5). This conceptualization traces the movement of a pathogen through the population. It begins with the reservoir from which the pathogen is transmitted by direct or indirect means to a susceptible host. It is instructive for our community preparedness work to break this down a little further.

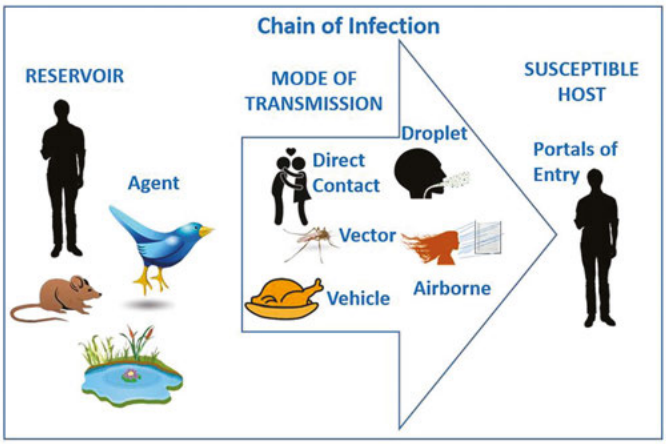

Image 1: Recreated from image developed by CDC http://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section10.html

Specifically, CDC outlines five components in the chain: reservoir, portal of exit, mode of transmission, portal of entry and susceptible host.

1. **Reservoir.** Here is where the infectious agent grows, lives, multiplies. Typically, a reservoir can be a human, an animal and sometimes the environment — for instance, the soil can be a source of fungal agents.

2. **Portal of exit.** This is the pathway by which a pathogen leaves the host. For instance, the respiratory tract is the exit portal for the flu, urine provides the exit for schistosomes and feces for cholera. Usually, the portal of exit correlates to the site within the reservoir where the pathogen is located.

3. **Mode of transmission.** CDC outlines two modes of transmission: direct and indirect.
   - Direct Transmission. Terminology can be confusing, but consider two forms of direct transmission:
     - o Direct contact. For instance, skin to skin contact, sexual intercourse and kissing.
     - o Droplet spread. Still considered direct transmission, this is generally short-range droplet spread, where, for instance, transmission occurs before droplets hit the ground. Sneezing and coughing produce such droplets.
   - Indirect Transmission. Here, an infectious agent transfers to a host by:
     - o Suspended air particles (as opposed to heavier droplet sprays). They can be blown over great distances and remain active for a long time.
     - o Inanimate objects, called vehicles. These include food and water, blood products and bedding.
     - o Vectors, which involve animate intermediaries. The many examples include mosquitoes, ticks and flies, which transmit infectious agents thought mechanical means. Biologic transmission, such as malaria parasites and guinea worms mature in an intermediate host before they can be transmitted to humans. They, too, are considered vectors.

4. **Portal of entry**. This is how a pathogen enters a host. The portal provides tissues in which the pathogen can survive and grow or where a toxin can act. CDC notes that the portal of entry is often the same as the portal of exit in the reservoir. For instance, the flu exits and enters the respiratory tract. Other portals of entry include blood, mucous membranes and the skin.

5. **Susceptible host.** This is the final link in the chain of infection. Many factors determine susceptibility, including genetic factors, a person's physical health, immune responses and other considerations such as conditions of the skin and gastric acidity.

The five modes of transmission selected for consideration in this project logically rely on the CDC's scheme for the chain of infection. We look specifically at transmission methods that can be manipulated to disrupt the transmission or minimize the probability that the pathogen can make its way from the reservoir to the susceptible host. The five include vector, human/animal, food, water and air.

Infectious illnesses

There is a seemingly endless list of infectious illnesses that stand to threaten local populations; an early challenge in this project was to select among the most

likely and most virulent diseases that could imperil the communities targeted for this project. We turned to several authoritative sources, including WHO, CDC and National Institutes of Health (11, 15), for insights into the initial round of training modules. We will continue to build this list over time, increasing the training tools available.

These disease modules are included in the initial module library.

Common diseases
Avian influenza
Cholera
Coronaviruses (MERS-CoV, SARS)
Ebola
Hendra virus infection
Influenza (seasonal, pandemic)
Leptospirosis
Meningitis
Nipah virus infection
Plague
Rift Valley fever
Smallpox and human monkeypox
Tularaemia
Viral haemorrhagic fevers (Ebola, Marburg, Lassa, Crimean-Congo haemorrhagic fever, etc.)
Yellow fever
Zika virus

Neglected tropical diseases
Buruli ulcer
Chagas disease
Dengue and Chikungunya
Dracunculiasis (guinea-worm disease)
Echinococcosis
Endemic treponematoses (Yaws)
Foodborne trematodiases
Human African trypanosomiasis (sleeping sickness)
Leishmaniasis
Leprosy (Hansen disease)
Lymphatic filariasis
Onchocerciasis (river blindness)
Rabies
Schistosomiasis
Soil-transmitted helminthiases
Taeniasis/Cysticercosis
Trachoma

Tropical diseases
Chagas
Dengue
Ebola
Helminthiasis
Leishmaniasis
Leprosy
Lymphatic filariasis
Malaria
Onchocerciasis
Schistosomiasis
Trypanosomiasis, human African
Tuberculosis
Hepatitis
HIV AIDS Series

The assembly and presentation of the training courses

WiRED's aim was to provide a training course, configured around the three items described above — user's group or role in the community, mode of infection transmission, specific disease. Given a starting list of 40 infectious diseases, six community groups or roles and five ways in which a disease can be transmitted, it became clear that the number of training courses for this assignment was overwhelming. How could we assemble these courses efficiently to provide a useful training program for people in these communities? Our computer programmers came up with a clever approach.

To begin, using WHO and CDC information, we configured the computer program to link each disease with its primary method of transmission. So, for instance, malaria is transmitted by way of a vector; cholera through water and food; Zika, now known to be transmitted by vector and human contact. This information for each disease was written into the computer program.

So, the computer program contained four categories of information:

1. Introduction to infectious diseases (standard for all audiences)
2. Group/community position of the user (six categories)
3. Mode of transmission (five categories)
4. Infectious diseases (40 initially–additional topics added over time)

What happens next?

On an interactive Web page (also downloadable and provided on thumb drives), the user checks two items: His or her community group (from #2) and the infectious disease expected in the community (#4).

The computer then instantly assembles the course by packaging and presenting four modules: (1) the introduction, (2) group-specific information for community preparedness, (3) transmission information and (4) a detailed description of the infectious disease. The information package is presented in this interactive template:

Example

The principal of a local high school has learned that a cholera outbreak has devastated a region 100 miles from her town and that local authorities (or country-wide agencies) have issued warnings about the disease for her region. The principal has read newspaper articles about the cholera outbreak, but she has questions about details of the disease, its potential impact on her community, how people in her town can minimize its impact and how they can prepare treatment facilities and obtain medical supplies and other resources to deal with it. Being a respected leader in the community and responsible for more than 250 students and teachers, she wants to know what she should do.

It's in such an instance that she could turn to the WiRED program. She can access the training material online. If she were in a location where the Internet was unreliable or unavailable, she could access the identical program from a thumb drive. The thumb drive could be prepared elsewhere and brought to her town or copied from other thumb drives containing this information. The infectious disease training program can be shared on laptops and tablets. There are no file copying restrictions, no user IDs or passwords; WiRED encourages free distribution.

With this program on her screen, the principal would enter data as they appear here:

After she submitted this form, she would immediately receive the following page, offering the compiled course. Note that it offers an introduction to infectious diseases, a module on community leaders' responsibilities, a module on vector borne diseases and a detailed module on cholera—its characteristics, signs and symptoms, diagnoses, treatments and means of prevention.

The principal can complete the course in one sitting, or she can finish portions of it at her convenience. Each module follows this format: it presents key concepts, then, using good practices of behavioral learning theory, it tests comprehension of those concepts in a brief multiple choice quiz. More concepts, more quizzes and then the module ends with a final exam that reviews all information in the module. The program immediately reports a final score. The modules will also offer her the ability to print PDFs of pertinent information to share with her community (transmission details, prevention techniques and so forth).

While the principal is taking the cholera course designed for community leaders, others in the community can take a course tailored for them — government leaders, people in the media, medical and health workers, people in the travel industry and the general public. The courses anticipate the concerted efforts of community members and provide specific advice for the six group categories suggested by CDC research.

Conclusion

The recent Ebola outbreak in West Africa has been the most vivid example in years of a devastating illness that can wipe out entire villages, cause panic across a continent and spread fear around the globe. Although less dramatic, influenza, cholera, measles and yellow fever offer other examples of epidemics this decade that have taken thousands of lives. Each case is different, of course, but a common thread running through all epidemics is the notion that a coordinated community-level response, joined with the assistance of global agencies, can significantly ease the intensity and spread of disease.

Two elements can determine the effectiveness of community preparedness for an epidemic: education and coordination of community resources. We approach our role in this matter by joining an extensive, computer-based library of health training modules with additional information about modes of transmission and responsibilities specific to key groups. Contingent on the user's community group and the expected infectious disease, a computer assembles the modular training units into a complete course. This is our offering to small communities in low-resource regions when they must deal with an approaching epidemic.

The program is easy to use, distribute and update. Users enter only two key details — their role in the community and the infectious disease — and the computer

immediately prepares the course. People then move from module to module and the computer keeps track of progress through the course. The computer also provides scores of final quizzes for each module.

The entire program is available online and can be downloaded to thumb drives, laptops or tablets for easy sharing and use in remote locations where Internet connectivity is absent or limited. This peer-reviewed and professionally prepared program is, of course, free of charge.

It is evident that communities often are poorly prepared for the onslaught of an epidemic. Much of their vulnerability is due to inadequate supplies and personnel, and this is where the global health community comes squarely into the frame. Outside groups can send in experts, a workforce, equipment, medical supplies and other resources no community can be expected to have in waiting.

Other vulnerabilities, however, have to do with inadequate knowledge about the infection and about how local communities can prepare for the challenges ahead. No community should stand alone against a major infectious disease, and our aim here is not to prepare them for such a thing. The purpose of this program is to give people in communities a head start, to help them know how they can resist the infection and how they can integrate their efforts with each other and with resources from the global health community.

Image 2: Shot P1 Empty

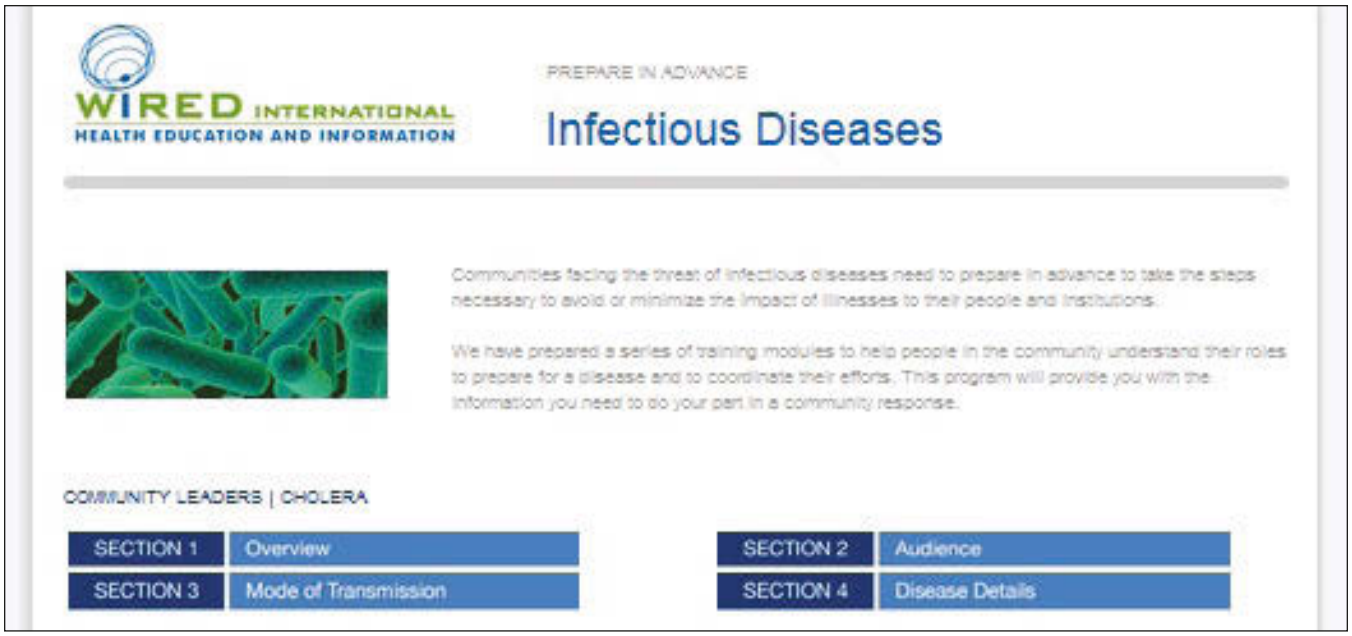

Image 3: Shot P2 Empty

Image 4: Principal and Cholera checked off

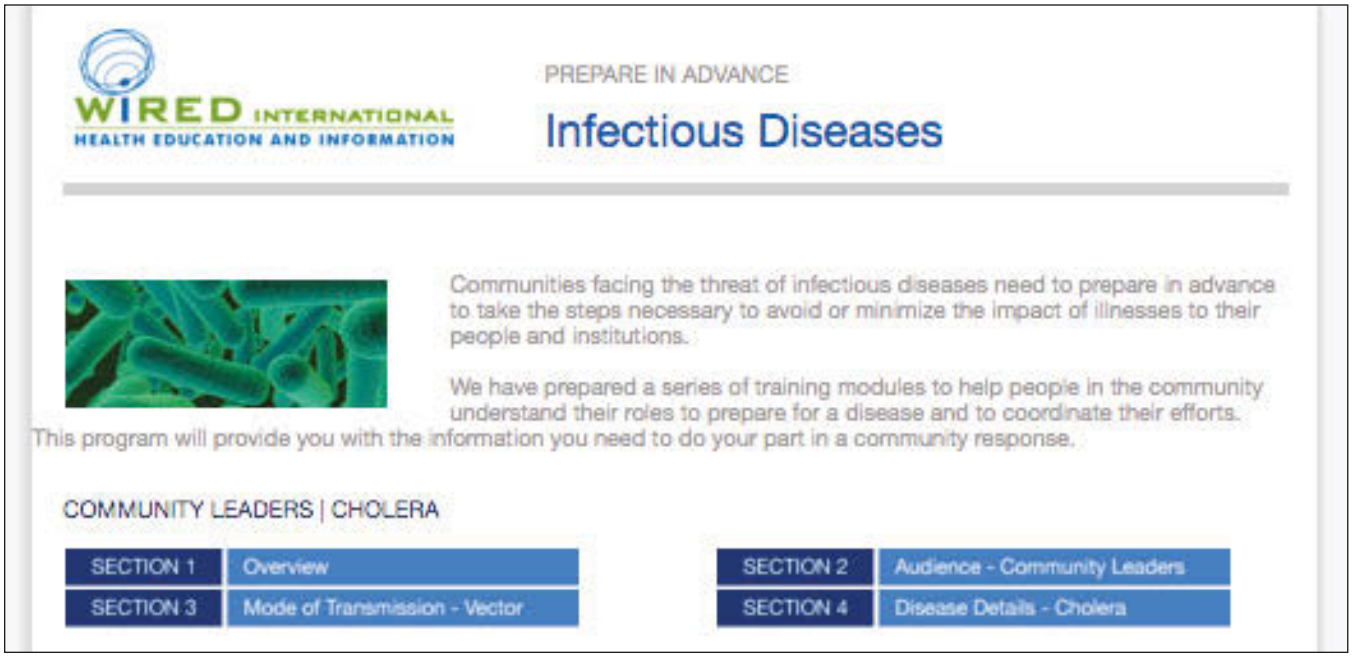

Image 5: Course compiled

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MINDFULNESS IN MEDICINE AND HEALTHCARE:
A Personal Introduction

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Abstract

Mindfulness meditation is a cognitive-behavioral intervention which shows benefits in a wide range of conditions. It is effective for stress reduction and lifestyle modification which are central to the treatment of many chronic diseases. Mindful practice enhances job satisfaction and counters burnout in medical professionals. The effects of mindfulness meditation are mediated through attentional networks and brain areas associated with stress processes, emotional regulation, learning, memory, and executive control. Mindful practice is relevant for both personal and professional challenges which many physicians face on a daily basis.

I clearly remember the bright summer day, climbing a cliff at the old quarry near my boyhood home, feeling for little nooks and ledges to carry me safely upward. Along the way I paused to catch my breath and admire below the view of the Arkansas river flowing away to the horizon and above me a hawk gliding on the wind. Out of nowhere a tiny ladybug in shiny orange and black landed on my outstretched arm, paused, and then flew off. Rested, I started back up, feeling the world at my fingertips.

In contrast to this vivid experience, I can remember arriving at the hospital one morning and realizing that I had been rehashing a recent case that did not go well. I did not recall much about my drive which I had made many times, although it routinely involved both travel at high speeds and grinding stop and go traffic. I assumed I had driven the whole way safely and nothing unusual had happened, but few details of the trip came to mind. I tried to focus as I stepped into the ER and the nurse handed me a chart.

As I recognize now, while both climbing and driving, my attention was guided by aspects of my experience that were in turn threatening, pleasant, or novel, their salience in the moment determined simultaneously at conscious and unconscious levels. (1) While climbing, a balanced sense of vigilance and calm prevailed. In technical terms, working memory and task-positive "attentional" brain networks were fully engaged. (2) In contrast, being on auto-pilot with mind wandering while driving involved the anticorrelated default mode network of the brain (DMN), which interferes with working memory and learning. (3, 4, 5) Mind wandering is a common mode of mental activity, active about 50% of the time as demonstrated in a study of over 2,000 adults sampled in real time. And it is more often than not associated with unhappiness. As the authors of the 2010 Science study conclude:

"A human mind is a wandering mind, and a wandering mind is an unhappy mind. The ability to think about what is not happening is a cognitive achievement that comes at an emotional cost." (6)

Such vast differences in the quality and potential consequences of normal wakeful states, either attentive or mind-wandering, raise an important question. How is

one to be aware in the moment whether one is paying attention to what one is doing or on auto-pilot with the mind wandering? Given the mind's tendency to wander, awareness and regulation of the attention is indeed crucial to anyone processing complex information and making vital, potentially life-altering decisions, whether one is climbing a steep cliff or driving to work. But how is one to know? In the words of William James,

"The faculty of voluntarily bringing back a wandering attention, over and over again, is the very root of judgment, character, and will. No one is compos sui if he have it not. An education which should improve this faculty would be the education par excellence. But it is easier to define this ideal than to give practical directions for bringing it about."(7)

Moving along a few decades in my story, I had been practicing emergency medicine and raising a family for some years. Multi-tasking had become routine. I felt preoccupied with diverse concerns and frequently under pressure, and had also developed some significant health problems. Although following my doctors' orders, there was little improvement in my condition. I suspected that stress itself might be an underlying factor and that the ways I have been accustomed to coping with life's challenges were no longer helping much. About this time one of my physicians suggested that I look into a course in stress reduction based on the practice of mindfulness, which had been developed at the Univeristy of Massachusetts Medical School. I had practiced meditation for periods of time in the past since learning it from a classmate in medical school, and I decided to give the program a try.

In the course I became more aware of the role of stress in my health, as well as the influence of a negative bias in my thinking. This well-recognized asymmetry in the way we use negative versus positive information to make sense of our world has been documented to be active from infancy. (8, 9) How influential this bias is, and how it is reflected in one's thinking and behavior, can make a profound difference in one's stress load and related physical and mental health. (10, 11) As I began noticing how active this bias was in my own thinking, I saw a tendency toward being critical and worried. Although written 500 years ago, Montainge's words described how my own thoughts were inclined: "My life has been filled with terrible misfortune; most of which never happened."

Mindfulness meditation is a prescription for relieving stress that can be traced back to the Buddha. It has been practiced widely in the East for millennia, and has been most highly developed in the Buddhist tradition. In 1979, Jon Kabat-Zinn, a molecular biologist interested in the mind-body connection to stress-related disease, removed the religious elements from the practice and developed a course on mindfulness as an approach to reducing pain and stress. (12) Physicians at the University of Massachusetts Medical Center began sending patients with a variety of stressful chronic diseases to the UMass Stress Reduction Clinic. In 1982, Kabat-Zinn published the first paper on mindfulness as a clinical intervention, showing significant benefits for patients with chronic pain. (13)

In this 8-week course * in the practice of mindfulness, I became more familiar with the nature of stress and what determines it, especially how highly individual it is. It brought home the meaning of Hans Selye's statement that "it is not the stress that kills us, it is our reaction to it". The course emphasized techniques designed to enhance awareness of stress and interrupt the stress reaction cycle. Meditation was taught as a way of settleing the mind and training the attention, including active monitoring and recogition of mind-wandering. In these practices I saw a way to handle the frequent worry and negative thinking that often ran in a discursive loop, especially when the mind was on auto-pilot. As I became more familiar with the technique of paying attention to my attention and attitude, I began noticing that I had more choices in stressful situations, with better options for responding rather than reacting more or less out of habit.

As I started approaching situations with a new perspective, I sensed a shift toward being more accepting and less critical. I also noticed a fresh approach to coping with situations I would have found frustrating or disappointing in the past, and being more inclined to be proactive about taking responsibility for my own outlook and well-being. Although stressful situations continued to be a regular part of life, practice and growing skill in reframing perceptions were showing me that stress was not what happened to me, but what happened in me, a product of attitudes and choices I was becoming more adept at recognizing.

The central practice of mindfulness for stress reduction is meditation, which is key for developing certain skills of awareness which can then be used in everyday situations, particularly stressful ones. Meditation itself is a formal exercise of attention-training aimed at strengthening one's core psychological capacities, including self-

regulation of thoughts and feelings, along with body awareness, especially of stress-related sensations. Mindfulness as a distinctive expression of awareness involves three components: 1) training the attention; 2) engaging a certain attitude- one that is open, curious and friendly, i.e. "non-judgmental"; and 3) being purposeful, i.e. having some recognizable intention, including why one is meditating in the first place. (14)

Mindfulness is an inherent trait (termed "dispositional mindfulness") which all people have in varying capacities, (15) which is modifiable, and which is associated with various markers of health and healthy behaviors. (16, 17, 18) The formal practice through which one cultivates this trait is mindfulness meditation, a technique of focused and relaxed attention to present-moment experience with an attitude of acceptance. Meditation is often done sitting quietly while focusing on the breath. Other mindful practices include moving meditation such as yoga and chi gong. Of various types of such practices, mindfulness meditation (in the form of MBSR and similar interventions based on it) has received the most attention in modern healthcare and neuroscience research. The number of articles on mindfulness in peer-reviewed journals has grown exponentially over the past four decades, marked by increasing methodological rigor as this field of study matures. (19, 20)

Individual intentions for practicing mindfulness vary, but as a clinical intervention, the primary goal is to obtain relief from stressful physical and mental symptoms. The methods of mindfulness involve training the attention in meditation for active awareness while reducing reactivity to negative stimuli. Mindfulness meditation and yoga (practiced as a mindfulness exercise) induce a set of intergrated physiologic changes termed the relaxation response, a hypothalamic-mediated reaction which results in decreased sympathetic nervous stress system activity, decreased heart rate, lower metabolism, and decreased respiratory rate. (21, 22, 23)

Stress-induced processes can be adaptive in the short term ("allostasis") but can lead to damange when stress is excessive ("allostatic load"). Consequently, allostasis and allostatic load jointly affect vulnerability to brain-dependent and stress-related mental and physical health conditions. These include impaired immunity, atherosclerosis, bone demineralization and metabolic syndrome. (24) In the brain, stress-induced plasticity, causing atrophy of nerve cells, is most prominent in the prefrontal cortex, hippocampus and other areas associated with fear-related memories and self-regulatory behaviors. (25, 26)

The brain is the central processor as well as target of stress signals and stress-related hormones. It determines what one will experience as stressful and how one will cope with stressful experiences. At the same time the brain changes both functionally and structurally as complex neural circuits coordinate behavioral and physiological stress response systems to meet the demands imposed by particular stressors. This dynamic activity involves bidirectional signaling between the brain and body.

As a target of stress, the brain undergoes functional and structural remodeling in response to stress which can lead to damage when stress is excessive. Critically, the prefrontal cortex, which is the most evolved brain region and supports our highest-order cognitive and executive functions, is also the brain region most sensitive to the detrimental effects of stress. Acute uncontrollable stress can cause a rapid and profound loss of prefrontal cognitive abilities, and more prolonged stress exposure leads to changes in prefrontal structure. (27, 28)

The cumulative damage of chronic stress (29) is described succinctly in a 2016 article in the journal Metabolism: "Stress and its related comorbid diseases are responsible for a large proportion of disability worldwide. Although the term 'stress' is used in a wide variety of contexts, it has consistently been demonstrated that individuals with stress and related disorders experience impaired physical and mental functioning, more work days lost, increased impairment at work, and a high use of health care services." (30)

`As methodolgically rigorous studies accumulate, the intersection of the role of stress in disease and the role of mindfulness as a clinical intervention becomes more clear. Mindfulness as a treatment for chronic pain offers a good example of how this research has developed over time. A current PubMed search of "mindfulness chronic pain" brings up 247 articles, ranging from Kabat-Zinn's 1982 study (13) to one in the current issue of the journal "Pain" describing significant improvments in chronic pain in patients who had taken the MBSR course (compared to a control group receiving usual care) mediated by factors including decreased catastrophizing, along with improved self-efficacy and acceptance. (31) In a 2016 editorial in JAMA reviewing the efficacy of mindfulness for chroinc pain, the authors comment: "For patients with

chronic painful conditions, options are needed to help them live with less pain and disability now. ... High-quality studies such as the clinical trial by Cherkin et. al. create a compelling argument for ensuring that an evidence-based health care system should provide access to affordable mind-body therapies." (32)

Besides being proven effective as an intervention in major disease entities, mindfulness has a demonstrated role in disease prevention. An analysis of the New England Family Study revealed that participants' mindfulness was found to be associated with factors involved in lowering cardiovascular disease risk, including high physical activity, non-smoking, weight, and diabetes. Reviewing this and other studies, the authors offer a consensus-based model for the clinical mechanisms of mindfulness in disease prevention and management, as supported by epidemiologic and neuroscientific evidence to date. They conclude that mindfulness is associated with and positively influences cardiovascular health through improved self-efficacy and self-regulation, associated with decreased craving, reactivity, and depressive symptomatology, which positively affect behavior regarding smoking, diet, exercise, and medication adherence. (34)

In other studies, mindfulness has been shown to be associated with recognized biopsychological factors involved in disease treatment and prevention which include i.) producing a relaxation response, ii.) decreasing sympathetic nervous system activity at the level of the brain (33), iii.) improving attentional focus (35, 36, 37, 38), iv.) increasing cognitive flexibility (39), v.) decreasing emotional reactivity (40, 41), vi.) improving conflict monitoring and reactive control (42), and vii. facilitating rational decision making. (43)

"Bottom-line" epidemiologic studies demonstrate significant benefits in reduced health care utilization associated with mind-body interventions which emphasize patient participation incorporating mindfulness and meditation. (44, 45) Most recently, Benson and colleagues examined healthcare "billable encounters" of patients (n=4,452) deemed "high utilizers" of medical services, compared to controls (n = 13,149) over 4 years, using an 8 week mind-body intervention combining mindfulness and relaxation training with other techniques to reduce stress and enhance resiliency. Total utilization for the intervention group decreased by 43% ($p < 0.0001$). Clinical encounters decreased by 42% and Emergency Department visits decreased from 3.6 to 1.7/year ($p<0.0001$) . Subgroup analysis (identically matched initial utilization rates of the intervention group compared to high utilizing controls) showed the intervention group significantly reduced utilization relative to the control group by 25% across all clinical categories. The authors concluded that such mind-body interventions are safe, effective and inexpensive relative to the usual cost of care: "the cost savings from reduced emergency room visits alone in the treatment group relative to the control group is on the order of $2360/ patient/year. ...Assuming median values for visits at these treatment sites (including outpatient care, urgent care and emergency department visits, and hospitalizations) gives an expected range of cost savings of $640- $25,500/ patient/year. … These estimates are rough and based on aggregate numbers but give a sense of the scale of the opportunities available." (46)

Any account of the impact of stress and the role of mindfulness would be remiss if it did not include some mention of the epidemic of professional burnout which is at an all-time high among physicians, and which begins in training. More than half of US physicians report symptoms of burnout, including 63% of family physicians, 69% of general surgery residents, and 71% of medical students. (47, 48, 49) In addition to the toll on the individual physician, this stress-induced syndrome of emotional exhaustion, depersonalization, and impaired sense of accomplishment is associated with suboptimal care and major medical errors. (50, 51) The sources of workplace stress for physicians are complex, and proposed solutions are equally complex and challenging given the dynamic and often competing forces shaping today's practice of medicine. (52, 53)

I am no stranger to burnout, but I have noticed that during periods when I have made time for regular meditation, things have gone better in my life: in my work, my relationships, in how I handle stress. My experience resonates with a 2009 report in JAMA which demonstrated that primary care physicians participating in a program focusing on mindful awareness experienced improved personal well-being, including burnout and improved mood, along with positive changes in empathy and psychosocial beliefs, both indicators of a patient-centered orientation to medical care. (54) As leaders in medicine call for changes to reduce demands on physicians, many see promise in the mounting evidence that mindful practice offers a unique approach for coping with the inherent stress of clinical care. (55, 56, 57)

Besides the benefits to well-being, I can concur with the results of these studies which show that being more observant and empathic are inherent to mindful practice. This would sometimes be affirmed in the ER after evaluating a patient and telling them what I thought was causing the headache or chest pain or abdominal pain or whatever it was that had brought them in. It was not unusual to have to say that I could not find anything conclusive in the labs and X-rays and EKG's that would explain their symptoms. After answering their questions the best I could and advising follow-up, I would not infrequently hear a patient thank me for seeing them. In a sense I felt that this confirmed that a crucial part of our encounter had occured- that of truly seeing this patient, and that this sense of being seen and heard was what most connected me as a physician with a human being who had entrusted life and limb to me, who was almost always a perfect stranger to them. I also believe it was this sense of connection which, despite the inevitable missed diagnoses and poor outcomes, played some part in there being no claims of malpractice from any of the thousands of patients I treated in a high-risk setting for over 30 years.

After life in the ER, I attended teacher training at the UMass Center for Mindfulness, and now only see patients in my role as an instructor of the Mindfulness Based Stress Reduction course. My students include many with diseases that have been reported on in studies of mindfulness referenced in this article, including chronic pain, cardiovascular disease, cancer, immune disorders, anxiety, depression, ADHD and PTSD. My experience in this role confirms what patients were told from the beginning in the Stress Reduction Clinic, that "it doesn't matter if you believe in the practice or not, it just matters that you do it". In this sense, mindfulness meditation is like physical therapy: studies show that the benefits flow from the exercise itself, and depend on effort rather than faith. (58, 59)

In 2007 NIH Director Elias A. Zerhouni, MD described the deep challenges facing healthcare: "We are in a revolutionary period of medicine.... As opposed to the doctor-centric, curative model of the past, the future is going to be patient-centric and proactive. It must be based on education and communication.... It requires voluntary, intelligent participation, not passive acceptance. We can provide the information, but you have to do something for yourself." (60) Physicians-in-training are increasingly being introduced to this patient-centered participatory model of care. Mindfulness-related training relflected in wellness programs and/or research can now be found at most US medical schools, and, increasingly, in residency programs. (61, 62)

Although meditation is the traditional core practice of mindfulness, there are many ways of cultivating this dispositional trait that is present in each of us, which is essentially an attitude toward experience. In this sense, anything that helps the mind become more aware of experience with acceptance becomes a mindfulness practice. This might include, for instance, such practices as reflective inquiry, compassion, gratitude, and active listening, as described in the 2009 JAMA article on "Mindful Practice". (54) In healthcare and society at large there is a growing appreciation for what mindfulness offers in response to the stress of modern life, beginning with the challenge we each share of living in a digital world with a stone-age brain. (63)

In an age of rapid change and continual uncertainty, we are often faced with new and at times unpleasant realities, and how we manage these circumstances becomes for each of us a question to some degree at least of how we shall adapt. In these times, the words of Viktor Frankl always seem relevant: "When we are no longer able to change a situation, we are challenged to change ourselves". (63) In my experience, mindful practice is an approach to the challenge which has stood the test of time.***

*MBSR is taught by instructors who have taken training through the Center for Mindfulness at the University of Massachusetts Medical School. The 8 week course meets once a week for 2.5 hours plus one 6 hour session, and involves attention training exercises which include sitting meditation, body scan meditation (focusing on bodily sensations as the attention moves from one body region to the next), and yoga (traditional postures and stretches designed to develop strength, flexibility and balance). MBSR also involves recognition of one's intention for practice as well as cultivating an attitude of acceptance and non-judgment as part of being present to one's experience in the moment. Besidies in-class meditation and discussion, there is daily at-home practice.

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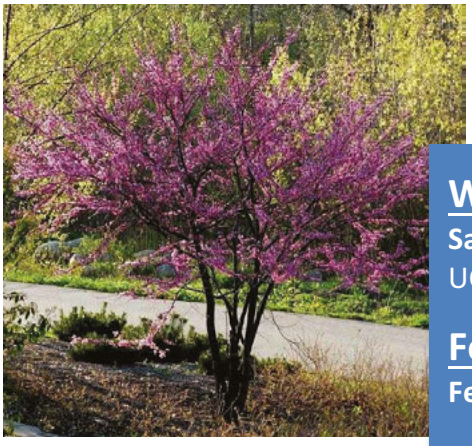
Mindful Practice in Medicine: An Introductory Workshop



Enhancing Quality of Care, Quality of Caring and Resilience

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Saturday & Sunday • February 4-5, 2017 9:00 am–5:00 pm
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To Register: http://mbpti.org/

A weekend retreat-like workshop followed by four live interactive 90-minute webinar sessions designed to improve the quality of care that clinicians provide while improving their own resilience and well-being. This workshop offers an experiential learning environment, with a focus on developing the capacity for self-awareness in stressful and demanding situations.

Designed for medical practitioners (physicians, NPs, PAs) and others involved in medical practice and education. *No prior experience is required.*

Course Directors: Ron Epstein, MD & Mick Krasner, MD

At the conclusion of this activity, participants should be able to:

- Increase self-awareness and self-monitoring during clinical work and teaching
- Attend to patient's needs, reduce and respond to errors, practice with greater effectiveness and compassion, and attend to their own well-being
- Incorporate mindful practice into clinical and educational activities at their home institutions

The Program includes:

- 2-day intensive workshop followed by 4 live, interactive 90-minute webinars with didactic and experiential components
- Eight learning modules integrating self-awareness and contemplative practices, interactive large group sessions, dyadic exercises incorporating narratives and appreciative inquiry dialogues, and small- and large-group discussion.
- Session themes include:

Noticing/Mindfulness	***Responding to Suffering***	***Errors in Medicine***	***Uncertainty***
Burnout and Resilience	***Meaning in Medical Practice***	***Aspiration: Realizing Values***	***Grief and Loss***

- Focus on "informal practices" that can help health care professionals deal with difficult situations during the workday and bring mindfulness into everyday clinical work

Dr. Ron Epstein has devoted his career to promoting physician self-awareness and effective communication in clinical practice. His current research is on improving communication about prognosis and treatment choices in cancer settings. He directs Mindful Practice programs, the Center for Communication and Disparities Research and the Deans Teaching Fellowship program at the University of Rochester School of Medicine and Dentistry where he is Professor of Family Medicine, Psychiatry and Oncology. He has published over 250 articles and book chapters. Ron Epstein's first book, *Attending: Medicine, Mindfulness and Humanity*, will be released in January 2017.

Dr. Mick Krasner is professor of Clinical Medicine at the University of Rochester School of Medicine and Dentistry, and practices primary care internal medicine in Rochester, New York. He has been teaching Mindfulness-Based Interventions to patients, medical students, and health professionals for more than 15 years, involving nearly 2000 participants, including over 600 health professionals. Dr. Krasner is engaged in a variety of research projects including the investigations of the effects of mindfulness on the immune system in the elderly, on chronic psoriasis, and on medical student stress and well-being. His personal mission is centered on compassion in medicine and envisions a health professional-patient relationship where healing is truly bidirectional, care goals are mutually derived, and the uniqueness of the clinical encounter reflects the central act of mutual high regard.

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*The NIH defines mindfulness meditation as one of a group of mind-body interventions that are "designed to facilitate the mind's capacity to affect bodily function and symptoms". The focus is on the interaction between the brain, body, and behavior, and is practiced with intention to use the mind to alter physical function and promote overall health and well-being. (49)

***If you would like to try a brief form of meditation, here is the "20 Breaths Meditation"

"20 Breaths" Meditation Instructions

The mindfulness practice described is called "20 breaths." This exercise helps you take a fresh start whenever and wherever you want. It teaches you to step away from the distractions, frustrations, irritations, and preoccupations that stress and exhaust us.

The "20 breaths" exercise is actually 20 separate mindfulness exercises. For 20 breaths you bring all of your attention to each breath just for the duration of that breath. Each practice only lasts about 5 seconds, which is how long a typical breath lasts. At the end of each breath, that period of mindfulness practice is over; you take a fresh start with the next breath. When that next breath begins, give it your full and complete attention. You do that 20 times, with 20 breaths.

Start by seeing what it feels like to pay attention to a single breath. Take an upright, balanced posture, close your eyes if that is comfortable for you, and in a moment, take a single breath, while giving it all of your attention. You can try it right now.

It's not hard, and of course, nothing dramatic happens, you are just noticing your breath, but you are doing something that most people have never tried. You are intentionally bringing all of your attention to what is happening in the present moment. You have started your training in mindfulness.

Try the same thing again, but this time, pay attention to three breaths. When you notice your first breath, see if you are giving it your full attention. Often we notice something without experiencing it fully. It is possible to practice mindfulness with only part of your mind. Obviously, that isn't our goal now. If you find that part of your attention is somewhere else on your first breath, see if you can bring more of your attention to the second breath. And finally, see if you can bring all of your attention, which is completely possible, to your third breath. See what it feels like to experience each breath a little more fully than the one before.

Gradually build up to 20 breaths. Or, if your day is very busy, do several practices of 3, 5 or 10 breaths during the day.

When you do the 20 breaths, each breath is a separate event, and each breath gets separate attention. At the end of the breath, you can let go of any effort. Relax, and the next breath will come. You will need to count the breaths to know when you are finished. So when you breathe in, and breathe out, you count it by saying the number "one" to yourself. After the second out breath, you count "two" and so on. When you get to "10", start counting back to "zero." So, for the first 10 breaths, you count from "1 to 10", and for the second 10 breaths, you count back from "9 to 0."

If you lose count, it's no problem. If you like, you can make your best guess as to where you were, and pick up there. Or, you can just start over as the whole exercise takes only a couple of minutes. As you do this, you might discover that it is harder to pay attention, even for only a few seconds, then you might have thought.

Sometimes, it seems as if every second has its own distraction and that the mind wanders constantly. Don't let it bother you. In fact, this is one of the most important things that this exercise teaches us. You begin to notice when you are distracted, and then step away from that distraction. If we are going to undo stress, distractedness, and tension, first it takes noticing that they are happening in the first place. Try not to give yourself a hard time, or struggle too much. A light touch and a sense of humor will help.

If you practice this everyday, soon you will find that it is possible to bring all of your attention back into the present moment even when you are very stressed and distracted. You won't do it perfectly every time, but with practice you will get better and better. Pretty soon you will be able to use this technique to find stillness and relaxation right in the middle of your busiest and most stressful day.

Adapted from Michael Baime, MD

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PERNICIOUS ANEMIA MIMICKING MYELODYSPLASTIC SYNDROME:
A Case Report

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Abstract

Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency due to lack of production of Intrinsic factor in the stomach. It is not that uncommon as we think, and is a fatal disease if untreated or mistreated. In this case report, I present a patient whose pancytopenia was misdiagnosed as Myelodydplastic Syndrome elsewhere. After this patient was correctly diagnosed as having pernicious anemia and treated with vitamin B12, the pancytopenia was completely resolved. It is extremely important to make a correct diagnosis of pernicious anemia because its clinical features are often overlapping with Myelodysplastic Syndrome.

Introduction

Megaloblastic anemia, regardless of etiology, was originally called pernicious anemia (PA) because they were fatal before treatment became available. Currently, the term "pernicious" is no longer applied for all megaloblastic anemias, but should be used for vitamin B12 deficiency due to the lack of production of the Intrinsic Factor (IF). Impaired IF production can occur in adults due to autoimmune destruction of parietal cells which secrete IF (1). Because untreated or mistreated PA is a fatal disease and treatment of PA is rather simple with vitamin B12, it is extremely important to make a correct diagnosis of PA. In this case report, I present a patient with PA who was initially diagnosed as Myelodysplstic Syndrome (MDS) as the patient's hematological manifestations mimic those of MDS with macrocytic anemia, pancytopenia, and even abnormal cytogenetics.

Initial Presentation

SK is a 71-year-old Asian woman who initially presented with pancytopenia: hemoglobin 9.1 g/dL, hematocrit 28.2%, MCV 146.6, MCH 48.7, MCHC 34 g/dL, platelet 61 K/uL, and WBC 3.0 K/uL.

The peripheral blood smear showed severe macrocytosis. Serum total bilirubin was 1.4 unit/L. The vitamin B12 and folic acid levels were 294 pg/mL and 21.7 ng/mL respectively.

She had bone marrow biopsy elsewhere, revealing hypercellular marrow with trilinage hematopoiesis. The flow cytometry showed abnormal myeloid maturation with the blast count of 3%.

The cytogenetic revealed abnormal female karyotype with the clonal deletion of chromosome 20: 46 XX, del(20)(q11.2q13.1). A diagnosis of Myelodysplastic syndrome (MDS) was made and treatment options with chemotherapy planned. At this point, her family physician sought a second opinion with a hematologist.

She had easy fatigability, frequent night sweats, nausea, abdominal discomfort and indigestion. She was slightly unsteady had has mild numbness of the legs and feet. No focal neurological deficits were detected. Her family history was not remarkable. She does not use alcohol or tobacco.

Her medication includes: amlodipine, raloxifen, omeperazol, and Bentyl (dicyclomin). Previous upper endoscopy revealed atrophic gastritis with negative H. pylori infection.

Physical examination showed pale conjunctiva, not icteric sclera, no peripheral lymphadenopathy, no hepatosplenomegaly, and mild mid-abdominal tenderness.

Hematological re-evaluation

Although her initial hematology features are consistent with MDS in view of pancytopenia, macrocytosis, hypercelullar bone marrow and abnormal cytogenetic study, I suspected that this patient has pernicious anemia in view of the extremely severe macrocytosis with MCV 146.6, occasional hypersegmented neutrophils seen by peripheral blood smear examination at the office laboratory, and high MCH with normal MCHC (Fig 1). The bone marrow aspiration smear also showed megalocytosis (Fig 2).

Therefore, intrinsic factor (IF) blocking antibody and parietal cell antibody were ordered. The IF blocking antibody test came back positive, and the parietal cell antibody was negative. Immediately, even before the antibody tests results returned, she was treated with cyanocobalamin 1000 µg SQ daily for a week, and then weekly for four weeks.

She felt well immediately after a couple of injections of vitamin B12. In particular, heavy night sweating disappeared and she regained the sense of well-being. The follow up CBC at 1 month after the cyanocobalamin therapy became normal: Hemoglobin 12.3 g/dL, hematocrit 36.8% MCV 112.6 fL, MCH 37 pg, MCHC 33.4 g/dL, platelet 125 k/uL and WBC 6.8 k/uL.

Discussion

Pernicious anemia (PA) is a macrocytic anemia due to vitamin B12 (cobalamin) deficiency, which, in turn, is the result of deficiency of intrinsic factor, a protein that binds avidly to dietary vitamin B12 and promotes its transport to the terminal ileum for absorption. The deficiency of intrinsic factor is a consequence of the presence of atrophic body gastritis (ABG), which results in the destruction of the oxyntic mucosa, and thus, the loss of parietal cells, which normally produce chlorhydric acid as well as intrinsic factor (2). PA is generally considered an autoimmune disease. The autoimmune origin of PA is based on the presence of parietal cell and/or intrinsic factor autoantibodies, and the frequent association with other autoimmune disorders, such as autoimmune thyroid disease, type 1 diabetes mellitus, and vitiligo (2). Whereas the disease originally was believed to be restricted primarily to whites of Scandinavian and Celtic origin, recent evidence shows that it occurs in all races as shown in this Asian woman. PA is usually under-diagnosed, and is not an uncommon problem in older adult subjects. In one series, the incidence of PA was 4.1 percent in white and black women and 2.1 percent in white and black men (3, 4).

The onset and progression of PA are very slow. As a consequence, patients often are not aware of their symptoms related to anemia, because over time they have become used to them. In many such cases, the underlying disease may not be suspected until CBC has been performed. However, patients with PA may seek medical advice due to non-specific symptoms related to the presence of anemia per se, such as weakness, asthenia, decreased mental concentration, headache, and

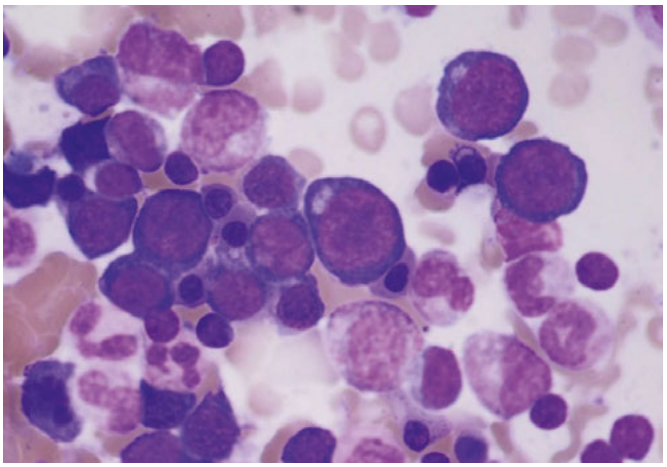

Fig 1: macrocytosis and hypersegmented neutrophil

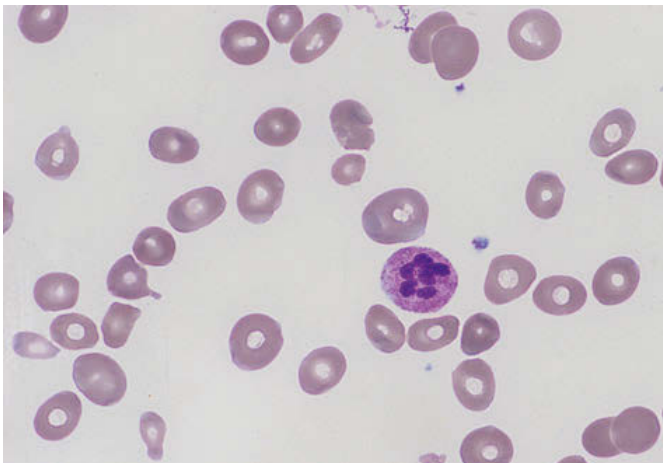

Fig 2: megaloblastosis of marrow cells

especially, in elderly patients, cardiovascular symptoms such as palpitations and chest pain (5, 6). Less frequently, patients with PA may present only with neurological symptoms, such as paresthesia, unsteady gait, clumsiness, and in some cases, spasticity. Indeed, vitamin B12 deficiency may cause peripheral neuropathy and lesions in the posterior and lateral columns of the spinal cord (subacute combined degeneration) and in the cerebrum, and these lesions progress from demyelinization to axonal degeneration and eventual neuronal death. It is particularly important to recognize these symptoms early, because the neurological lesions may not be reversed after replacement therapy with vitamin B12 (5, 6).

Schilling test was the confirmatory diagnostic test which proves IF deficiency. To confirm that the cobalamin deficiency is the result of intestinal malabsorption due to intrinsic factor deficiency, urinary excretion of orally administered vitamin B12 is low, and is increased by administration of vitamin B12 and intrinsic factor. Unfortunately, the availability of this test is obsolete due to problems related to its radioactive reagents. Therefore, in clinical practice, the presence of intrinsic factor deficiency may not be proven, and increasing reliance is placed on the detection of intrinsic factor antibodies for the diagnosis of PA, which are viewed as useful markers of this disease (5). Recently a study reassessing the diagnostic performance of IF and parietal cell antibodies in PA patients was done (7,8), which yielded, for IF antibodies, a sensitivity and specificity of 40-70% and 100%, respectively, and for parietal cell antibodies, a sensitivity and specificity of about 80% and 90%, respectively. It should be mentioned that, in order to diagnose vitamin B12 deficiency, total vitamin B12 measurement is used cost-effectively as the parameter of choice, but it has limited sensitivity and specificity, especially in persons with vitamin B12 concentrations in the lower reference range.

In general, serum vitamin B12 levels can be interpreted, as follows (10):

- >300 pg/mL – Normal result; vitamin B12 deficiency unlikely
- 200 to 300 pg/mL – Borderline result; vitamin B12 deficiency possible
- <200 pg/mL – Low; consistent with vitamin B12 deficiency (specificity of 95 to 100 percent)

Metabolite testing can be done for those patients in whom a high degree of suspicion of vitamin B12 deficiency is present, especially those with borderline serum vitamin B12 levels. Serum concentrations of homocysteine as well as serum and urinary concentrations of methylmalonic acid (MMA) are elevated in vitamin B12 deficiency; but homocysteine is also elevated in folate deficiency.

As described above, the presence of anti-intrinsic factor (IF) antibodies is highly confirmatory for the diagnosis of PA. Elevated serum gastrin levels, low pepsinogen I levels, and a low ratio of pepsinogen I to pepsinogen II are highly sensitive for the diagnosis of PA (90 to 92 percent), although these tests lack specificity. Addition of these tests may help to make the diagnosis of PA in those patients who do not have anti-IF antibodies. As alternative, modern biomarkers for early diagnosis of vitamin B12 deficiency, such as holotranscobalamin, also known as active B12, as well as methyl malonic acid as a functional B12 marker, have been proposed (8).

Accurate differential diagnosis of other causes of cobalamin deficiency is mandatory. Vitamin B12 deficiency may result from other causes of impaired absorption in the stomach or intestine, or by decreased intake due to vegetarianism (Table 1). Dietary cobalamin (Vitamin B12) is bound to salivary proteins, Haptocorrin (R-Factor), which needs to be cleaved in the presence of chlorhydric acid in the stomach before it can be bound to IF and be absorbed in the terminal ileum (11). Therefore, prolonged intake of antacid medications such as proton pump inhibitor can cause vitamin B12 deficiency. Chronic metformin use for diabetes results in vitamin B12 deficiency in 30% of patients (12). Vitamin B12 deficiency, which may present without anemia and as a peripheral neuropathy, is often misdiagnosed as diabetic neuropathy, although the clinical findings are usually different. Failure to diagnose the cause of the neuropathy will result in progression of central and/or peripheral neuronal damage which can be arrested but not reversed with vitamin B12 replacement (12). One very important note, when patients with PA are treated with folic acid, the macrocytic anemia may improve, but the neurological deficits by PA deteriorate and become irreversible (13). Interestingly, PA is associated with chromosomal abnormalities, which makes clinicians more confused as various chromosomal abnormalities are common in MDS. Chromosomal abnormalities in PA are usually corrected quickly with vitamin B12 treatment (14, 15). As a clinical hematologist, I often discovered that patients with vitamin B12 deficiency from various causes (Table

1) often present normocytic anemia when they have co-existing iron deficiency because iron deficiency causes microcytosis of RBCs.

In summary, a patient with PA who was misdiagnosed as having MDS was treated successfully with vitamin B12 with complete resolution of pancytopenia and neurological symptoms. Hematological pictures of PA mimic those of MDS; macrocytic anemia, neutropenia, thrombocytopenia, and abnormal cytogenetic study with chromosomal abnormality. As untreated or mistreated PA is fatal, it is extremely important to make a correct diagnosis of PA.

(Table 1)

Causes of Vitamin B12 deficiency

Gastric abnormalities
Pernicious anemia
Gastrectomy/bariatric surgery
Gastritis
Autoimmune metaplastic atrophic gastritis

Small bowel disease
Malabsorption syndrome
Ileal resection or bypass
Crohn's disease
Blind loops
Diphyllobothrium latum (fish tapeworm) infestation

Pancreatic disease
Pancreatitis
Pancreatic insufficiency

Diet
Strict vegans
Vegetarian diet in pregnancy

Agents that block or inhibit absorption
Neomycin
Biguanides (eg, metformin)
Proton pump inhibitors (eg, omeprazole)
Histamine 2 receptor antagonists (eg, ranitidine)
N2O anesthesia inhibits methionine synthase
Inherited transcobalamin II deficiency

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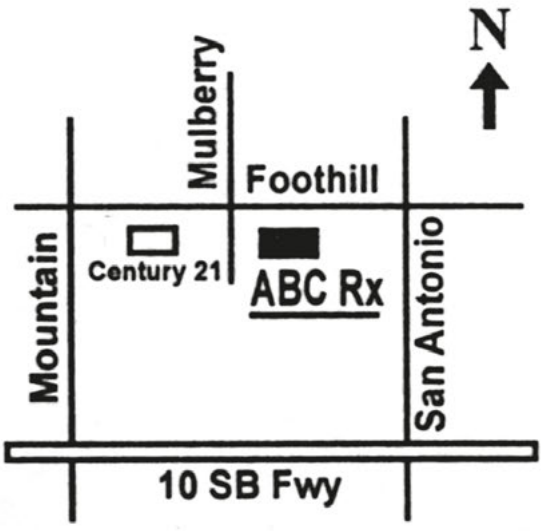

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