What's in a Name???

GOOD - authentic, honest, just, kind, pleasant, skillful, valid

NEIGHBOR - friend, near

ALLIANCE - affiliation, association, marriage, relationship

CORPORATION - company, business establishment

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I recently saw a patient who had abused a drug which was not included on the usual toxicology “screen” sent from the emergency departments (ED) of most American hospitals. What made this case important to me was that one of the parents, a physician, told the ED doctor what drug to look for; and when the tox screen came up negative, the patient was then thought to have a neurological disorder and referred to me.

The doctor hadn’t thought to check what drugs the tox screen tests for and what drugs are missed. As it happens, the targeted drug, dextromethorphan, which is the single most abused drug by children in the United States, does not appear on the usual tox screen so that an “extended” or “complete” tox screen must be requested. I thought this mistake so important that I published a report in a neurology journal to call attention to the ED oversight. What happened next is what’s bizarre.

As a result of this report I was contacted by two major drug companies that market cough medicines containing dextromethorphan. I was to report to the Food and Drug Administration an adverse effect of the drug! Now, who, in their right mind would consider an intentional overdose for the effect of getting high a side effect? And didn’t I already exceed my civic duty by publishing the case so that anyone at the FDA and anyone who can read English would be able to find the effects of this drug with a computer search? What was the point? There is a reason for post-marketing surveillance, possibly even decades after a drug is released, but the FDA has become increasingly disinterested in true post-marketing surveillance, having caved in to Big Pharma. But what is learned from another case of purposeful drug toxicity? Do breweries have to report every case of drunkenness that they hear about? People may drink beer to get drunk. It’s not a side effect.

I was annoyed but not dismayed. This came later. I became a site investigator for a pharmaceutical company’s study of a prodrug of gabapentin, to be used to treat restless legs syndrome. This drug has a different kinetic profile, making it possibly superior, possibly not, but at least different from a patent viewpoint. More of a “me too” sort of drug than a breakthrough. But I was surprised when I read the protocol. The FDA had required safety testing that was far more complex than what was needed to demonstrate that the drug was effective. What is bizarre is that the safety data required had no justifiable basis. In fact, one could argue convincingly that the extensive data on gabapentin should have made it easier rather than harder to demonstrate safety in the case of this newer drug. Maybe to compensate for their weak post-marketing work they are doing as much as they can pre-approval? From an investigator’s standpoint, the only outcome of the mandated testing will be a higher price for the drug when it comes to market.

This caused me then to reflect on a study I designed for my own center. It required FDA approval for testing an old drug on a new patient population. To test low doses of extended-release ropinerol, doses which we routinely give to PD patients in their 60’s or 70’s, in a schizophrenic population, of physically healthy people decades younger than the PD patients, the FDA asked us to give the dose in the office and monitor the subject for eight hours. This will, of course, make recruitment incredibly difficult. How many people are willing to be in a trial if they have to hang around a doctor’s office for eight hours getting blood pressures measured every hour? And what sort of safety data will be gleaned from this when there is a decade of experience using the drug at similar doses in older, frailer patients?

Just recently I completed a “study” in which I asked one hundred consecutive patients with Parkinson’s disease if they had a problem with a runny nose. If they did I then asked if it developed before, with or after the PD. If the patient was accompanied by anyone over the age of 50 I asked that person too if they had a runny nose. To be “ethical” I prefaced my first question with the statement that I was doing a survey, which was a research study to determine if a runny nose was more common in PD than in people without PD. Of course I had a strong suspicion that this was the case but it’s never been a published observation, although an ENT colleague told them that it’s a well known observation in his field. This isn’t the idiotic question you may think it is. For one thing it turns out that it may be very embarrassing. For another patients and families are generally very pleased to know when some oddball symptom is “part” of the disease and that they are not being hypochondriacal or “weird” in some way. In this case it turned out to be about ten times more common in PD patients than the controls. This probably has some clinical importance in that this is most likely the result of early sympathetic dysfunction that may, in fact, precede the motor signs of the disease. If true, this would provide another “pre-symptom” of the disease that will be helpful when we find a drug that slows the disease progression. The result was submitted as a letter to the editor of a prestigious journal. The journal was very interested, asked a number of questions, but refused to consider a revision when they learned that I had not obtained Institutional Review Board approval. I was not surprised, but had decided a priori to “test” whether common sense was a consideration in contemporary academic medicine. I then consulted the IRB about the study. The response was, “You don’t need IRB approval for a study of this sort, unless you want to publish it. Many journals require IRB approval for any study.” When I submitted the protocol the IRB stated that I needed to hand the patient a single page stating what I was studying and that they didn’t need to participate. As Dave Barry says, I am not making this up.

There have been a lot of problems in the clinical trial arena. There is no question that doctors and pharmaceutical companies have, on occasion, abused their subjects. It is clear that clinical trials need to be policed. It is also clear that the FDA needs to monitor drug safety and that they need to be assid-
Blessed Are the Pure In Heart

There was a time in the distant past when the heart ruled all.

But this was before prosaic scientists envisaged the heart as a convoluted muscular pump conveying blood through a succession of four inner chambers with intervening valves, its rhythmic contractions governed by electric stimulants and its substance nourished by two critical arteries. The motivating currents came to be measured, the patency of the coronary arteries determined and amazing interventions then brought this muscular contrivance, when ailing, back to a reasonable state of normal function.

The downhill odyssey of the heart, from its role as a wondrous spiritual organ to that of a robotic mechanism, is now virtually complete. An American company recently assembled an artificial heart, will all its internal valves, that is said to be capable of replacing the human heart. No longer, then, is the heart the seat of joy, sorrow and intervening emotions. No longer can the Scriptural Proverbs declare that “A merry heart maketh a cheerful countenance, but by sorrow of the heart the spirit is broken.”

The fragile voice of the poet, exclaiming that the heart is more than a mute, compliant muscle, has now been overtaken by the authoritative declarations of science. Angioplasty, the rerooting of the coronary arteries, has proven its worth and, accordingly, its superiority over Wordsworth’s sonnets.

The heart, in truth has been the poet’s most reliable, most enduring metaphor. It is doubtful that there is any human emotion, from the most evil to the most pious, that has not been ascribed to the human heart. The heart has been the seat of understanding, the source of interpersonal warmth, a place of benevolence and the seat of yearning.

We humans regularly experience a change of heart, or worse, a heart chilled by fright, shrunken by sorrow, bleed in despair or weakened by a loss of resolve; but still it remains the ultimate source of courage. Robert Burns, the Scot with a sunny disposition, saw the heart as the site of kindness and benevolence, most resembling God. Yet others envisioned the organ as mean-spirited, capricious and hard-hearted. Even Exodus beheld a Pharaoh’s heart which had hardened.

Dostoevski imagined the heart as the arena where God and the devil fought combat, “and their battlefield is the heart of man.” Long before angiography was invented, Ibsen, that northern cynic, declared: “Look into any man’s heart and you will always find at least one black spot which he has to keep concealed.” Faulkner agreed, stating that the heart is where life’s truths and verities are closeted.

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The heart is an organ that wearies easily, but still, in Wordsworth’s words, it remains “a fountain of sweet tears, and love, and thought, and joy.” It is a mobile organ that a credulous lover might give away and a sophisticated suitor might casually accept. It can be the site of utter purity; although even a president of sterling character might commit adultery in his heart. [This was long after Matthew had asserted that he who looks upon a woman with lust has already committed adultery in his heart.]

The mobility of the poetic heart is truly astonishing: sometimes it lies deeply embedded within a fierce bosom, sometimes it is worn upon one’s sleeve and sometimes, in times of terror, it migrates to one’s mouth. At other times, as in the poetry of Macloed, it can be a lonely hunter that hunts upon a lonely hill. On rare occasions, according to Spenser, it might be a source of nutrition: he stated “to eat thy heart through comfortless despair.” The anatomic site of the heart may be in some doubt, but to some unpoetic individuals rendering advice to young women, the way to a man’s heart is through his stomach.

The heart, despite its occasional heaviness, can sometimes be lifted with joy, bonded to one’s very being [heart and soul] and yet in times of stress can be weary, humbled, despairing and contrite. And it can be an organ of uncommon eloquence, as in the Book of Job, “I caused the widow’s heart to sing for joy.”

Washington, our first president, was remembered by Henry Lee when he referred to him as first in the hearts of his countrymen. The third president, Thomas Jefferson, saw an anatomical channel between one’s words and the moral status of the heart. [“Falsehood of the tongue leads to depravity and falsehood of the heart.”]

Nor have the poets ignored heart disease. Did not the Psalms talk of a broken and contrite heart? And did not Shakespeare’s Lear confide that his heart would break into one hundred thousand fragments? Even cardiac flutter and fibrillation were known to the poets long before the electrocardiographers demonstrated pathologic arrhythmias. Crane declared: “I linger on the flathouse roof, the moon-light is divine/ But my heart is all aflutter like the washing on the line.”

But sometimes insubstantial ideas, mere poetry, validate themselves long after they have been discarded by the practical people of the world. An extensive epidemiological study, conducted by a team of Canadian physicians, tracked 50,000 Ontario patients, each older than age 70, with demonstrated heart disease. They found that recurrent heart attacks, particularly fatal episodes, were 27% more common on these patients’ birthdays. Similarities, these patients were more vulnerable to cerebral stroke on their birthdays than on any other day of the year. The researchers found no correlations between birthdays and the onset of other organic diseases such as appendicitis. They ascribed this “birthday effect” to “psychosocial stressors” but acknowledged that other forces might be implicated, perhaps even partying and transient overindulgence. Sentimentality, a very unscientific premise, was never mentioned.

And finally a study, back in the 1980s, analyzed 22,000 Rhode Island death certificates, demonstrating a relative paucity of deaths just prior to one’s birthday followed by a sudden spike in deaths on or just beyond the birthday.

The poetic eye may indeed be more discerning, more discriminating, than all the awesome instruments of modern medicine.

— STANLEY M. ARONSON, MD

— JOSEPH H. FRIEDMAN, MD
**Spotlight on Claudication: An Important Disease Gets Attention**

Timothy P. Murphy, MD, Gregory Dubel, MD, James Bass, MD, Sun Ho Ahn, MD, Gregory M. Soares, MD, and Joselyn Cerezo, MD

**Peripheral arterial disease (PAD) affects 5% of those over the age of 50 and up to 29% of those over the age of 70.** Claudication, the most frequent symptom of PAD, consists of pain in the leg muscles during walking, usually in the calf. US census data indicate that the number of Americans over the age of 65 is expected to double by 2030, and the incidence of PAD is expected to increase as our population ages. Those with claudication experience an increased relative risk of total mortality that is 2 to 4 fold greater than those without claudication, and have 6-year survival of only 55%, and 10 year survival of only 37%.

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health recently recognized the importance of furthering research and education about PAD. The NHLBI has increased funding for PAD-related research, and has committed to funding a public health awareness campaign about PAD (www.aboutpad.org). This article will review advances in management of intermittent claudication, the most frequent presentation of PAD, and discuss new research that will broaden our knowledge base in this area.

**The Impact of Claudication**

Claudication is a marker for increased risk of cardiovascular disease and stroke, and is a chronic disease that can profoundly limit physical functioning. Reduced physical activity in older individuals is associated with increased markers of cardiovascular disease risk, such as high blood pressure, diabetes, obesity, systemic inflammation, thrombosis, and disorders of lipid metabolism. Physical activity is known to be inversely associated with cardiovascular events. Walking disability caused by PAD results in a sedentary lifestyle, self-perceived walking disability, and lower health-related quality of life. In summary, claudication precludes an active, healthy life-style in many individuals that may contribute to the observed excess mortality in this population.

**Recognition of Claudication**

In an era when medications that address symptoms were of limited effectiveness, the risk of morbidity and mortality were not well known, and when the only revascularization option was surgery, diagnosing and treating claudication was not a high priority in medicine. However, over time compelling arguments for identification of claudication patients have emerged. First, quality of life studies are increasingly showing the claudication population to have very low physical quality of life, comparable to congestive heart failure. Figure 1. Second, numerous studies have demonstrated the risk of heart attacks, strokes, and death to be similar to those with known coronary artery disease, and medical risk factor reduction has become increasingly sophisticated and recommended for claudicators. Finally, if revascularization is necessary, the value of interventional therapy is currently widely accepted and has 90% less risk than surgery. The contemporary practice of medicine requires the importance of PAD to be appreciated and thoroughly considered, diagnosed, and managed routinely.

**Diagnostic Evaluation**

Claudication usually can be readily diagnosed by history and physical examination; the ankle-brachial index (ABI) examination is done to confirm the clinical impression. Other diagnostic tests such as magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) provide precise anatomic vascular images which can be used for treatment planning, particularly for those patients considered for revascularization. In the past, the more elaborate diagnostic examinations were often the purview of the vascular specialist, but increasingly these tests are being ordered or performed in the primary care setting. In fact, in order to achieve the goal of increased recognition and risk factor management for individuals with claudication, evaluation and medical management in the primary care setting is essential. A multispecialty consensus panel recently issued recommendations on the evaluation and management of patients with intermittent claudication.

**Management of Claudication: Risk Factor Modification**

Patients with PAD should have aggressive medical management of blood pressure (systolic blood pressure goal of <140 mm Hg, or 130 mm Hg if diabetic or chronic kidney disease), serum cholesterol (LDL <100 mg/dl)(ideally <70 mg/dl)
Table 1. Guidelines for Evaluation/Management of Claudicants

1. Claudicants should undergo a vascular physical examination including measurement of the ABI.
2. The ABI should be measured after exercise if resting index is normal.
3. Arterial imaging should not be performed in patients with normal ABI’s except when other pathology (e.g. popliteal entrapment) suspected.
4. Patients considered for revascularization procedures must have significant functional impairment and reasonable likelihood of symptomatic improvement and absence of other exercise limiting disease.
5. Patients offered revascularization procedures should
   a. be provided information of supervised exercise and pharmaceutical therapy
   b. receive comprehensive risk factor modification and antiplatelet therapy
   c. have significant impairment not allowing work or important activities
   d. have anatomy favorable to successful and durable revascularization

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claudication precludes an active, healthy life-style in many older individuals that may contribute to the observed excess mortality in this population

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gible. However, newer drugs have clear and proven clinical benefit in patients with claudication. Cilostazol (Pletal, Otsuka Pharmaceuticals), a phosphodiesterase inhibitor whose mechanism of action on claudication is unknown, has been shown to improve walking ability 40-60% in people with claudication. Cilostazol is prescribed as 100 mg twice daily, and is contraindicated in those with congestive heart failure. The most frequent complaint with cilostazol is headache, which may occur in a quarter of patients. If headache occurs, the dose can be reduced to 50 mg twice a day (the pills will need to be scored and cut in half) for two weeks, and if headache improves, a trial of increasing the dose to 100 mg twice a day can be done, or the dose can be continued at the reduced dose.

Exercise therapy results in significant improvement in walking ability when conducted in a supervised setting, but on average not when patients are instructed to exercise on their own. However, dedicated patients will report improvement in symptoms even from home-based programs. Supervised exercise re-habilitation, which has proven benefits in patients with claudication, is not reimbursed by Medicare or most private insurance, but is available in Rhode Island for participants in the National Institutes of Health CLEVER (Claudication: Exercise Vs. Endoluminal Revascularization) Study (see below).

Supervised exercise therapy and interventional treatment both have the potential of substantially greater improvement in walking ability than medication alone. How do they compare to each other? The roles of angioplasty and exercise for claudication have been the subject of a Cochrane Database Review. This review presented data from two studies that randomized claudication patients to angioplasty or other treatment. Results between the two studies were not consistent at 6 months, with the Edinburgh study showing better exercise performance in the angioplasty group, but the Oxford experience showing better results of exercise.

**The NIH Claudication Study**

Given the limited evidence supporting arterial stenting for claudication, and the risk and expense of invasive revascularization procedures, the National Institutes of Health funded a multi-center randomized clinical trial to study claudication treatment known as the CLEVER (Claudication: Exercise Vs. Endoluminal Revascularization) Study. The CLEVER Study has four treatment groups: optimal medical care (OMC), OMC plus supervised exercise rehabilitation, OMC plus stent, and OMC plus supervised exercise rehabilitation and stent. OMC will include cardiovascular risk factor modification including cholesterol, blood pressure, and diabetes management, dietary consultation, and smoking cessation. Approximately half of the participants will participate in supervised exercise training for 6 months without charge. Additionally, claudication medication (cilostazol) is provided for all participants throughout the study without charge. This comprehensive OMC meets and exceeds the multispecialty consensus panel recommen-
Table 2. Optimal Medical Management for PAD/Claudication Patients

1. Antiplatelet therapy-reduces the risk of MI, stroke, or vascular death in PAD patients
   • Aspirin 75–325 mg/daily
   • Clopidogrel 75 mg/d effective alternative and improves walking distance in many patients

2. Supervised Exercise-useful initial treatment for claudicants
   • minimum of 30–45 minute session
   • minimum of 3 sessions per week
   • for a minimum of 12 weeks

3. Hypertension management-reduces the risk of MI, stroke, CHF, and CV death
   • Goal of <140/90 mm Hg in nondiabetics
   • Goal of <130/80 mm Hg in diabetics or those with chronic renal disease
   • Use of ACE inhibitors in claudicants reduces the risk of adverse cardiovascular events.
   • ß-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated in patients with PAD.

4. Lipid Management—indicated for all patients with PAD
   • HMG-CoA reductase inhibitor (statin) indicated for all patients with PAD
   • Target LDL cholesterol <100 mg/dL

5. Smoking Cessation-patients should be:
   • Advised by each of their clinicians to stop smoking
   • Offered comprehensive smoking cessation interventions, including behavior modification therapy, nicotine replacement therapy, or bupropion.

CONCLUSIONS

Prior to the availability of effective medications to treat claudication symptoms, the evolution of minimally invasive interventional treatment options, studies of important quality of life issues for many patients with claudication, and appreciation of the need for aggressive risk factor modification, claudication was often underestimated in medicine. Fortunately, its prevalence and importance is being increasingly recognized, and public health awareness efforts focusing on claudication sponsored by the federal government through the National Institutes of Health should further recognition of this important disease. Ground-breaking research is ongoing in the pivotal NIH CLEVER Study, which should definitively determine optimal patient management for many years to come.

REFERENCES


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Update On Idiopathic Pulmonary Fibrosis: The Role of Gamma Interferon and Cytokines
Napoleon A. Puente, MD, Jason M. Aliotta, MD, and Michael A. Passero, MD

Idiopathic Pulmonary Fibrosis (IPF), one of the Idiopathic Interstitial Pneumonias (IIP), represents a challenge to clinicians because it is difficult to diagnose, has an unfavorable prognosis and no treatment is available to reverse or at least stop the progression of the disease. The etiology and pathogenesis of IPF are not completely understood.

Evolution of the Classification of Idiopathic Interstitial Pneumonias
Noble and Homer reviewed the history of changing concepts of IIP. They described how the classification of IIP has evolved since first described by Hamman and Rich between 1941 and 1943. Liebow and Carrington presented a new classification in the 1960s that correlated histopathological findings with disease prognosis.

In 1998, Katzenstein and Myers presented a new classification and more recently in 2002, the American Thoracic Society and the European Respiratory Society published a multidisciplinary consensus for the classification of IIP that defined the clinical diagnosis, the radiographic findings and the observed pathological pattern.

The most common and severe form of IIP, Idiopathic Pulmonary Fibrosis (IPF), is defined by certain histological features including areas of fibrosis with honeycombing adjacent to areas of normal-appearing lung and the presence of fibroblast foci. Fibroblastic foci are microscopic areas rich in mesenchymal cell proliferation and extracellular matrix that resemble wound healing. The heterogeneity of these findings (honeycombing and fibroblastic foci) is a hallmark for the morphologic description of Usual Interstitial Pneumonia (UIP), the pathology found in those with IPF.

In Respiratory Bronchiolitis (RB), there is an intraluminal accumulation of macrophages in the respiratory bronchioles, alveolar ducts and peribronchiolar alveolar spaces. Mild inflammation and fibrosis can also be seen. RB is known to be associated with smoking.

In Desquamative Interstitial Pneumonia (DIP), diffuse involvement of the lungs is seen with accumulation of macrophages in the lumens of distal airspaces. Fibrotic thickening of the alveolar septa and lymphoid aggregates can also be found. These changes are present in a more uniform pattern.

Diffuse Alveolar Damage (DAD), found in Acute Interstitial Pneumonia (AIP), is a diffuse disease that occurs in two phases. First, in the exudative phase, hyaline membranes, edema and interstitial acute inflammation are seen. The organizing phase occurs later and is characterized by loose organizing fibrosis, especially in the alveolar septa, and type II pneumocyte hyperplasia.

Nonspecific Interstitial Pneumonia (NSIP) features a broad spectrum of histological presentations with varying degrees of fibrosis or alveolar wall inflammation. There are usually no fibroblastic foci and honeycombing is absent.

Cryptogenic Organizing Pneumonia (COP) occurs in a patchy distribution with organizing pneumonia that involves alveoli, alveolar ducts and bronchioles. Inflammatory cells within the interstitium, type II alveolar metaplasia and an increase in alveolar macrophages are found. One of the important features of this disease is the relative preservation of the lung architecture.

Lymphoid Interstitial Pneumonia (LIP) is defined by infiltrates that are comprised primarily of T lymphocytes, plasma cells and macrophages. In addition, MALT (Mucosa Associated Lymphoid Tissue) hyperplasia is seen, typically, in an alveolar septal distribution.

Pathophysiology of Interstitial Pulmonary Fibrosis
Pulmonary Fibrosis is thought to be the late stage of a defective inflammatory response within the lung that is characterized by abnormal repair of damaged tissue with increased extracellular matrix deposition, vascular remodeling and fibroproliferation. The end result is the substitution of functional lung with scar tissue. Inflammation may arise in response to a variety of traumatic, allergic, infectious, toxic or autoimmune factors. However, the reason why the lung reacts in a way that causes fibrosis instead of normal repair of functional lung tissue is unknown and is the target of many investigations.

The major proinflammatory factors in the lung include interleukin (IL)-1, IL-6, IL-8, monocyte chemoattractant protein-1, tumor necrosis factor, macrophage inflammatory protein 1, macroph-

Table 1: ATS/ERS Classification of Idiopathic Interstitial Pneumonias

<table>
<thead>
<tr>
<th>Pathologic Findings</th>
<th>Clinical Diagnosis</th>
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<tr>
<td>Usual Interstitial Pneumonia (UIP)</td>
<td>Idiopathic Pulmonary fibrosis (IPF)</td>
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<tr>
<td>Respiratory Bronchiolitis interstitial pneumonia (RB-ILD)</td>
<td>Respiratory Bronchiolitis (RP)</td>
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<td>Desquamative Interstitial Pneumonia (DIP)</td>
<td>Desquamative Interstitial Pneumonia (DIP)</td>
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<td>Diffuse Alveolar Damage (DAD)</td>
<td>Acute Interstitial Pneumonia (AIP)</td>
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<td>Nonspecific Interstitial Pneumonia (NSIP)</td>
<td>Nonspecific Interstitial Pneumonia (NSIP)</td>
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<td>Organizing Pneumonia (OP)</td>
<td>Cryptogenic Organizing Pneumonia (COP)</td>
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<td>Lymphoid Interstitial Pneumonia (LIP)</td>
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age-colony stimulating factor, transforming growth factor and platelet derived growth factor. Although all of these factors have been found in animal or human models of pulmonary fibrosis and possess growth, differentiation, chemotactic and remodeling capabilities, it is not known how these factors specifically interact.

Lukacs et al reviewed the roles of T helper type 1 and type 2 cells in response to injury. When naïve CD4+ T lymphocytes are activated by an antigen, they can differentiate into two major subsets of T helper cells: T helper type 1 (Th1) cells (type 1 response) or T helper type 2 (Th2) cells (type 2 response). Each subset of cells secretes distinct cytokines that produce a different immune response. Th1 cells synthesize macrophage activating factor, IL-2, IFN-γ, lymphotoxin and TNF which promote cell-mediated inflammatory immune response, mainly against intracellular pathogens. Th2 cells secrete IL-4, IL-5, IL-10 and IL-13 which activate B cell antibody production such as IgG and IgE, and stimulate the differentiation and maturation of eosinophils, providing strong humoral and antiparasitic responses.

An effective response to an antigen requires the activation of Th1 cells and Th2 cells to produce both cell mediated and humoral immunity. If one of the subset’s production is unregulated or inappropriate, the end result may be harmful, such as the Th1-induced autoimmune response (type 1 diabetes, multiple sclerosis, rheumatoid arthritis) or the Th2-induced allergic response (IgE production and eosinophil activation in asthma).

In IPF, the type 1 response is thought to modulate tissue repair after a specific injury and reestablish normal functional lung tissue, in contrast to the type 2 response, which promotes extracellular matrix deposition and hence, fibrosis. The type 2 response cytokines IL-4, IL-10 and IL-13 have been identified to promote the activation of fibroblast and the production of fibroblast-derived extracellular matrix. The type 2 response predominates in IIP, suppressing the type 1 response cytokines, IFN-γ and IL-12.

**Role of IFN-γ in the Pathophysiology of Pulmonary Fibrosis**

IFN-γ is a cytokine that possesses antifibrotic, antiproliferative and immunomodulatory effects.

Gurujeyalakshmi and Giri demonstrated that in mice with bleomycin-induced fibrosis, treatment with IFN-γ caused a decrease in the accumulation of collagen in the lung, compared with untreated bleomycin-injured mice.

**... future therapeutic modalities used in the treatment of pulmonary fibrosis could potentially take advantage of the observed role of CXCR3 and its ligands**

Ziesche et al were the first to examine IFN-γ therapy in patients with IPF. Nine patients were treated with a combination of IFN-γ 1b and corticosteroids and nine were treated with corticosteroids alone. After 12 months of follow up, patients that received the combination therapy had significant improvements in total lung capacity and resting and ambulatory partial pressure of arterial oxygen compared to those receiving corticosteroids alone. Raghu et al later published a double-blinded, multinational trial of 330 patients with IPF who were unresponsive to corticosteroid therapy. One cohort was given IFN-γ 1b therapy and the other received placebo. It was concluded that patients receiving IFN-γ 1b didn’t show any improvement either in progression-free survival, pulmonary function or quality of life compared to controls. Subgroup analysis suggested that patients with better compliance to therapy may have benefited; however, investigators could not determine whether they responded better because they tolerated the side effects of IFN-γ better leading to improved compliance or because the subgroup suffered from less severe lung disease.

The Inspire (International Study of Survival Outcomes in Idiopathic Pulmonary Fibrosis with Interferon Gamma-1b Early Intervention) trial is ongoing. This will be the largest clinical trial ever conducted to evaluate the use of IFN-γ 1b therapy in IPF, hoping to provide a more definitive answer to the utility of this novel therapy.

**The links between IPF, IFN-γ and Chemokines**

Cellular movement plays a fundamental role in processes such as inflammation and immune surveillance. Chemical mediators, like chemokines, induce a receptor-mediated cytoskeletal response to produce a directed cellular locomotion. Chemokines are a group of chemotactic cytokines that have heptahelical G-protein-coupled receptors, many of which bind to more than one ligand, giving them multiple functions.

Four families of chemokines have been identified based on the number and position of their conserved cysteine residues: 1) CXC or the alpha chemokine family has two N-terminal cysteine (C) residues separated by one non-conserved amino acid residue (X), 2) CC or the beta chemokine family has two N-terminal cysteine residues in juxtaposition, 3) C or the gamma chemokine family has a single cysteine residue in the conserved position, and 4) CX3C family has two N-terminal conserved cysteine residues separated by three non-conserved residues.

The CXC chemokine receptor 3 (CXCR3), expressed primarily on Th1 cells, may play an important role in the regulation of pulmonary fibrosis. CXCR3 is a receptor for a family of ligands that are upregulated by IFN-γ 1b. These ligands include: 1) the IFN-γ induced protein 10-kDa, also known as the CXC chemokine ligand 10 (CXCL10), 2) the monokine induced by IFN-γ or CXCL9 and 3) the IFN-inducible T cell α chemotactrant or CXCL11.

In a bleomycin-induced pulmonary fibrosis model, Jiang et al found accelerated progression of fibrosis and increased mortality in CXCR3-deficient mice when compared to wild-type (WT) mice. They observed that in the absence
of the CXCR3 receptor, recruitment of the Natural Killer (NK) and CD8+ lymphocytes was defective after the bleomycin-injury. These mice had fewer NK cells in their peripheral blood, uninjured lung and other organs including the liver. These findings suggest that the CXCR3 receptors may play a role in NK and NKT cell homeostasis and may have a direct impact on the pathogenesis of fibrosis in response to injury.

Jiang et al.8 also reported a decrease in resident NK cell-produced IFN-γ levels found in the bronchoalveolar lavage (BAL) fluid of bleomycin-injured CXCR3-deficient mice compared to WT mice. In addition, they were able to demonstrate partial reversal of fibrosis in bleomycin injured CXCR3-deficient mice with the injection of exogenous IFN-γ or CXCR3+ leukocytes producing endogenous IFN-γ.

A link between chemokine receptors and pulmonary fibrosis may also exist in human pulmonary fibrosis, as described by Pignatti et al.9 They found decreased expression of CXCR3 and one of its ligands CXCL10 in BAL fluid CD4 T cells of patients with IPF compared to patients with other pulmonary disorders. This suggests that CXCR3 may play a protective role in the onset and the progression of pulmonary fibrosis and that CXCR3 and CXCL10 levels may help to predict response to IFN-γ therapy.

In conclusion, future therapeutic modalities used in the treatment of pulmonary fibrosis could potentially take advantage of the observed role of CXCR3 and its ligands. To date, IFN-γ injections have not been shown to benefit patients with IPF, in spite of promising data obtained from animal injury models.

Nonetheless, further research is needed to better understand the relationship between IFN-γ and CXCR3 and how this impacts the pathogenesis of pulmonary fibrosis. In addition, a variety of other drugs are being investigated for the treatment of IPF. (Table 2)

**REFERENCES**


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On Headache Tablets: Headache Incantations From Ur III (2113-2038 BC)

Vlad Zayas, MD

A recently published monograph by Johannes J.A. van Dijk and Markham J. Geller on Ur III (2113-2038 BC), contains two headache incantations. These scholars translated and analyzed the tablets from the Frau Hilprecht-Sammlung collection in Jena. The geographic source of the tablets is the Sumerian city of Nippur. The age of these two incantations is determined by the nature of the excavation site and the grammatical structure of the text.

Much accumulated medical, judicial, mathematical and artistic knowledge has been salvaged from excavations in the Mesopotamian city-states, including the Sumerian city Ur. Mesopotamia and especially Sumer has been called "the cradle of Western civilization."

The writing system developed in Mesopotamia, called cuneiform, required a clay tablet marked with a stylus. That marked tablet was then baked. This technique preserved an enormous amount of written materials from many periods of Mesopotamian history including Ur III (2113-2038 BC). However, significant numbers of tablets remain uncatalogued and are still not translated. The medical history of Sumer therefore remains somewhat fragmented. It is outside the scope of this article to discuss a full historic picture of medicine in Mesopotamia. This may be found in several large works on the subject.

There were two types of Mesopotamian medical practitioners: ashipu—a sorcerer, who dealt with magical aspects of the treatment, and an asu—a medical practitioner who provided pharmaco-therapeutic treatments including herbal concoctions, bandaging, plasters etc. The exact degree of the interaction between these two branches of Mesopotamian medicine remains unclear. It is unknown whether only ashipus were allowed to convey therapeutic incantations. Multiple therapeutic incantations in the medical armamentarium were directed against snakebites, paralysis and headaches. (A large collection of incantations for headaches is in preparation for publication).

The first incantation in the monograph is called “Amar-Suen’s Headache” – HS 2438, Ni 2187: (Figure 1)

The headache (-demon) is directed towards the man, the headache-demon is set to distress the neck muscles. There is no small opening which can ensnare the galla-demon, no binding can be tied on the headache(-demon). It is the young lad who is seized by the headache-demon, it is the young maiden whose diseased neck twitches. Asalluhi sent someone to his father Enki, (saying), say to my father: The headache (-demon) [is directed toward the man], [it is set to] distress [the neck muscles].’ [Enki answered] his son, ‘My son, what do you not know?’ ‘Why…, what can save him?’ (After) you have brought the purifying water, and you have poured fat of a pure cow, then let one rub (him) with that oil.’ Asalluhi son of Enki May the headache-demon ‘split the river bank’ on (the patient’s) cranium, may (the demon) break up like a pot. It is the incantation of Nin-girimma. It is the spell of Eridu, shrine of Enki.

The second incantation is called Namtar-demon vs. headaches – HS 1588+1596: (Figure 2)

In heaven the wind blows, on earth the mice proliferate, and Namtar inflicts headache. In men’s bodies is found beer, the south wind blows sag-duru on the (alluvial) land. In the mountains, the south [wind] blows the scattered seed. He (the patient) put his trust into (divine) standard. Therefore, the gods of heaven were afraid, they came down from (lit.’in’) heaven, the gods of earth were afraid, and were standing around the grave, the great gods themselves made (funerary) offerings. The fish in the river were afraid, and left their habitat, the birds in the heaven were afraid, and smashed into the base of the mountains. The undomesticated animals, creatures of the steppe and wild animals suffered from catalepsys [a disease of domestic animals]. Šakan was afraid and retired to the horizon, Nanna was afraid, and retired to the height of heaven. Asalluhi came to his father Enki, and he said, ‘My son, what don’t you know? What can be added to it?’ The god reconciled the sick man towards the steppe. Purify … [in a pure] place, take … of the pen and sheepfold which is not abandoned, choose a …lamb, choose … a black’ goat.

Discussion

Both incantations follow the same standard medical incantation formula – "Problem, Dialogue and Ritual Solution." The problem is first described. Then Asalluhi presents the problem to his father, the god Enki, who offers the therapeutic regimen for the problem. The first incantation is better preserved
There is only one previous Sumerian written mention of headaches in the epic poem *Enki and Ninhursag.* The two lines are: (In Heaven) “the sick-eyed says not ‘I am sick-eyed’/the sick-headed (says) not ‘I am sick-headed’”. The description of the headache in the first incantation offers a more detailed picture of the headache including the “distress the neck muscles”. The unrelenting nature of the headache and blowing motif is reminiscent of the more recent Mesopotamian incantation: “Headache rothem over the desert, blowing like the wind…” (Frequently, the age of this particular incantation is mentioned as 3000 BC. The primary source of this quotation is *The Devils and Evil Spirits of Babylonia* by R. C. Thompson (3). He states that the documents “were drawn up … about the first half of the seventh century before Christ”. He speculates, however, about possible previous recensions of “not less than six thousand years old”).

It is not entirely clear whether these texts describe a primary headache disorder or a secondary headache due to a catastrophic intracranial process (e.g. infectious or hemorrhagic). Other sources regarding Mesopotamian medicine reveal that medical practitioners were familiar with “continuous” as well as recurrent headaches.6

One of the approaches toward these texts is to see them in the light of today’s medical paradigm. It is tempting to label these headaches with current medical terminology as a particular type of headache as some authors do. These translations are imperfect, frequently leading to a scholastic discourse and disagreement among the Sumerologists. The tablets are often fragmentary, cryptic and poorly preserved. Usually, this leads to an unsuccessful search of the pharmaco-therapeutic effects of the ingredients used in the ritual (“pure cow” and “purifying water” in this case). Another approach is to analyze these as a part of magical medicine with diseases caused by demons and gods. Yet another approach is to view this as a literary document inspired by certain events, or as medico-poetics.

It is tempting to label these incantations as the first recorded descriptions of headache treatment (either magical or therapeutic). Therapeutic options for headaches are also present in Ancient Egyptian papyri. The oldest Papyrus Ramessum III is dated 1800 BC (4). However, both sources—Egyptian papyri and Sumerian clay tablets—are the copies of even older documents (possibly, as far as 3rd millennium BC). Therefore, the exact age of the original texts remains unclear. Within the limitations of the dating of the sources available, this is the first description of headache therapy. As it has been noted by S.N. Kramer in his comments on another Sumerian pharmacopoeia tablet, the exact proportions of the ingredients were not mentioned.6 This, he speculates, could be due to the desire of the medical practitioner to protect the trade secret from either the lay public or from his colleagues.

As the first people to develop writing, along with many other “firsts,”6 the Sumerians provided us with a first written word for a headache—“sag-gig” (below in the cuneiform).7

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The expectation for physicians at large is that they will act in a compassionate manner so as to facilitate the patient’s well being. The overwhelming majority of physicians certainly do, but according to recent studies there is a thankfully small but nonetheless increasing trend for some individuals to deviate from this standard, thus earning the moniker “disruptive.”

Historically physicians were offered a great deal of latitude regarding their professional behavior in hospital and office settings. Patient care and an arduous, high-stress professional lifestyle provided ample justification for these bad behaviors. Many have commented, if half in jest, that certain maladaptive personality traits if not frank personality disorders were actually requisite for success in certain areas of practice.

Fortunately, healthcare has evolved considerably over the past few decades and organizations are now much less tolerant of unprofessional disruptive behaviors by healthcare providers. Fellow professionals on multi-disciplinary teams see the importance of effective interpersonal skills, and adherence to high professional standards; and now hold members accountable. The practice of medicine has become increasingly complex and, in the interests of patient safety, medicine can no longer afford to countenance tantrums, outbursts, intimidation or a host of other disruptive behaviors by physicians or other allied healthcare professionals.

Despite a greater awareness of this type of professional misconduct and the presence of effective community based resources, many problem physicians are never referred for appropriate evaluation and treatment.

...medicine can no longer afford to countenance tantrums, outbursts, intimidation or a host of other disruptive behaviors by physicians...

Current Standard

Per AMA opinion E-9.045, disruptive behavior by physicians is defined as “Personal conduct, whether verbal or physical, that negatively affects or that potentially may negatively affect patient care constitutes disruptive behavior. This includes but is not limited to conduct that interferes with one’s ability to work with other members of the health care team. However, criticism that is offered in good faith with the aim of improving patient care should not be construed as disruptive behavior.”

The Commonwealth of Massachusetts Board of Registration in Medicine adopted a policy on disruptive physician behavior in 2001 that recognized the AMA opinions and linked disruptive physician behavior to patient safety, citing the Institute of Medicine finding that healthcare systems must promote teamwork and a collaborative approach to problem solving if medical errors are to be reduced. Unfortunately despite increased attention to this problem it remains a frustrating one for hospitals, Medical Boards and other healthcare organizations.

In Rhode Island, such behavior can be reported to one of two professional organizations with statewide scope. The Board of Medical Licensure and Discipline (BMLD) is a part of State government with a primary role to protect the public and to provide appropriate reper- cussion if a physician is not meeting a minimum standard of care. This regulatory body is composed of 6 physicians (including MDs and DOs) and 6 members of the public, including a plaintiff’s attorney and a hospital administrator as well as three others not involved in healthcare. Complaints reach the BMLD regarding physician practice from a variety of sources including dissatisfied patients, concerned colleagues and healthcare organizations. The BMLD is empowered to order medical and mental health evaluation; The BMLD may also sanction as appropriate for unprofessional conduct. The BMLD also facilitates an active, non-public diversion program that supports physician health in conjunction with the Physician’s Health Committee [PHC] sponsored by the RI Medical Society.

The PHC has achieved considerable success in the areas of physician impairment relating to substance abuse, psychiatric or medical illness and is also able to accept referrals regarding disruptive physician behavior. The BMLD, hospitals, physicians, allied health care providers and members of the public may make referrals directly to the PHC. The PHC will then direct evaluation and, as necessary, treatment and monitoring.
Scope of the Problem

The scope of the problem is considerable. One-third of hospital executives surveyed by the American College of Physician Executives reported weekly or monthly problems relating to disruptive physician behavior; 95% at least on a yearly basis.4

Many physicians have engaged in behaviors that may be considered disruptive on a particular occasion. However, physicians who consistently demonstrate these behaviors while few in number can have widespread impact on a hospital staff or in a practice group. Unfortunately, while most hospital executives, hospital chiefs or senior nurse managers could agree on the identity of disruptive physicians on a medical staff, few individual behaviors rise to a sufficient level to warrant specific discussion. Only the most egregious examples lead to formal sanctions reported to State Medical Boards. Consequently, it is very difficult to gauge the severity of the problem across healthcare settings.

The Underlying Cause

Disruptive physician behavior can be the result of psychiatric or medical illness, substance abuse or personality disorders or even the occasional acute life stressor such as a divorce or family death. In these situations addressing the root cause can be effective.

It must be recognized that specific disruptive behaviors such as angry outbursts may be precipitated by genuine system problems that impact upon patient care such as a systems-based medication or treatment error. Unfortunately in the wake of disruptive behavior the focus often shifts away from a legitimate care problem due to the physician’s disproportionate or misdirected response; a tragic missed opportunity to improve a system after an error.

However, while physicians exhibiting disruptive behavior often benefit from a medical and forensic psychiatric evaluation, they often do not have diagnosable medical or psychiatric illness. For this reason maladaptive personality traits and poor coping skills that may fuel the inappropriate behaviors become the focus for corrective efforts. Fortunately insight-driven psychotherapy, behavioral therapy and lifestyle changes can be effective for a motivated individual.

Recommended Approach

An institutional approach consistent with the AMA policy on Disruptive Physicians can be summarized with the help of the “10 R’s.” (Table 1) First, an institution must develop a system of Recognition predicated on a set of agreed upon definitions or descriptions of disruptive behavior. Such behaviors must be Reported via an established process that appropriately Records the event, assures confidentiality, and initiates a process to Review and verify the report(s). Once verified, determination of Responsibility through assessment for underlying cause should be done. Such determination may require a forensic medical and psychiatric evaluation towards the ultimate goal of development and implementation of a Remediation plan.

Subsequently, there should be a formal process for Rechecking (i.e. monitoring) behaviors and Reinforcement of improved interpersonal strategies. Resorting to discipline should be reserved for truly egregious disruptive behaviors or for individuals who have failed after an earnest attempt at remediation. Resources should also be identified in advance.

Conclusion

Physicians and allied healthcare providers who exhibit disruptive behaviors represent an important concern for everyone. Healthcare teams create numerous professional interdependencies that require appropriate professional interactions between providers as a necessary condition for effective patient care. Professional interactions characterized by respect foster good communication. Unfortunately, for a variety of reasons some healthcare professionals have difficulty meeting these communal standards of behavior.

It is incumbent upon all of us to address these behaviors assertively and to hold all healthcare providers to a high standard of professionalism. It is important that the entire medical community be aware of both the negative impact of disruptive behaviors and the importance of engaging institutions, the BMLD and the PHC to effectively address them.

Table 1. 10 R’s

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<thead>
<tr>
<th>Recognition</th>
<th>Report</th>
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<td>Record</td>
<td>Review and verify</td>
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<td>Responsibility</td>
<td>Remediation plan.</td>
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<td>Rechecking (i.e. monitoring)</td>
<td>Reinforcement of improved interpersonal strategies.</td>
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<tr>
<td>Resorting to discipline</td>
<td>Resources</td>
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A 56 year old woman with a past medical history of hypertension, hyperlipidemia and tobacco abuse presented to the hospital with progressive, aching chest and epigastric pain of 3 weeks duration associated with dyspnea on exertion. She denied palpitations, syncope, orthopnea, paroxysmal nocturnal dyspnea or edema. Her presenting vital signs were within normal limits. On physical exam she had mild jugular venous distention and an otherwise normal cardiopulmonary exam. Her laboratory values were remarkable for modest elevation of liver transaminases as well as elevations of cardiac enzymes (CK-564 IU/L, CKMB-45.9 NG/DL, troponin-232.3 NG/DL). Her electrocardiogram revealed normal sinus rhythm, left anterior fascicular block, non-specific ST-T wave abnormalities and decreased voltages in the precordial leads. (Figure 1)

She was taken electively to the cardiac catheterization laboratory. A right heart catheterization was performed. Her right atrial pressure was 16mmHg with a prominent x and y descent. Her right ventricular pressure was 27/18 mmHg. Her pulmonary artery pressure was 27/15 mmHg with a mean of 21mmHg and oxygen saturation of 55%. Her pulmonary capillary wedge pressure was 16mmHg. The left ventriculogram revealed normal left ventricular function (ejection fraction 60%) without any wall motion abnormalities. Her coronary angiogram showed normal epicardial coronary arteries. A transthoracic echocardiogram revealed normal left ventricular wall thickness, chamber size and function; there were no valvular abnormalities, pericardial effusion, or echocardiographic evidence of constrictive pericarditis. There was echocardiographic evidence of a severely dilated and hypokinetic right ventricle. (Figure 2) Given the isolated right ventricular dysfunction, a helical chest CT scan was performed to exclude pulmonary embolism and was normal. A repeat echocardiogram revealed worsening RV dilation and dysfunction with new moderate LV dysfunction (LVEF= 35%) when compared with the study from a week prior. The decision was made to perform right ventricular endomyocardial biopsy. The pathology was consistent with Giant-Cell myocarditis (Figure 4).

DISCUSSION

Giant-Cell myocarditis (GCM), also known as Granulomatous myocarditis, is a rare and frequently fatal disease affecting primarily young to middle-aged adults. The patients usually present with rapidly progressive congestive heart failure or symptoms of acute coronary syndrome. Patients may present with heart block, refractory ventricular arrhythmias or sudden death. Right heart catheterization, coronary angiography and endomyocardial biopsy are required to make the diagnosis. Right heart catheterization usually reveals signs of biventricular dysfunction. Coronary angiography usually reveals normal coronaries but there have been case reports of moderate to severe coronary disease superimposed on the myocarditis. A myocardial tissue sample is the only definitive way to diagnose GCM. Histopathologic features are characteristic with areas of wide spread or multifocal myocardial necrosis, rich cellular...
as sarcoidosis, systemic lupus erythematosus, inflammatory bowel disease, malignant thymoma, thyrotoxicosis, drug hypersensitivity and infections such as tuberculosis and syphilis.\textsuperscript{1} GCM is a very rare disorder and its epidemiology and pathogenesis were not well studied until a Multicenter Giant Cell Myocarditis registry was developed in 1995.\textsuperscript{1} The cumulative literature of GCM has data on fewer than 100 patients.\textsuperscript{1} The study consisted of 63 patients with biopsy proven GCM and has provided important data on prognosis and treatment. Untreated Giant-Cell myocarditis carries an 89\% mortality rate in its first 3 months\textsuperscript{1} with patients rapidly deteriorating to severe biventricular dysfunction and ultimately cardiogenic shock.\textsuperscript{2} Problematic, sustained refractory ventricular arrhythmias occur in 50\% of GCM cases at sometime during their acute illness.\textsuperscript{1}

Because of the infrequency of the disease, clinicians have limited evidence on which to base treatment. Conventional therapy for LV dysfunction should be given to all GCM patients with the exception of digoxin. Digoxin has been shown to increase mortality in these subsets of patients. Because of the presumed pathogenesis of GCM, immunosuppression with T lymphocytic cytolytic therapy as a treatment option has been studied. Immunosuppression has shown to be effective in the treatment of GCM as compared to placebo.\textsuperscript{1,6} The Multicenter Giant Cell myocarditis study group found favorable outcomes with combinations of corticosteroids combined with cyclosporine, azathioprine, OKT3 (muromonab-CD3) but not with steroids alone.\textsuperscript{1} Combined immunosuppressive therapy has shown a prolonged survival rate of twelve months compared to average three month survival in placebo.\textsuperscript{1} Combined immunosuppression has the ability to prolong survival and thus potentially allow cardiac transplantation to be performed. Cardiac transplantation is frequently required because of failure of immunosuppressive therapy.

The Multicenter GCM investigation suggest that early orthotopic cardiac transplantation is the treatment of choice for most GCM cases.\textsuperscript{1,2} As soon as the tissue diagnosis of GCM is made, patients should be placed on the transplant waiting list and transported to a clinical site that can offer ventricular support.\textsuperscript{2,5} GCM transplant recipients should be monitored much more closely and frequently than traditional transplant recipients because GCM can recur and clinical status can deteriorate quickly if intervention is not taken. Transplantation for GCM has produced survival outcomes similar to patients with transplant for idiopathic cardiomyopathy. Unfortunately, of the 34 patients in the GCM study who received cardiac transplant, GCM recurred in 9 patients and 1 patient died. GCM recurrence after transplant has been successfully treated with a strategy of more aggressive immunosuppression.\textsuperscript{1,4,5}

This case report highlights two important teaching points. First, to our knowledge, this is the first case reported in the literature, of Giant-Cell myocarditis initially presenting as isolated right ventricular dysfunction. Second, the case stresses the crucial role of early endomyocardial biopsy in severe or rapidly progressing myocarditis; this is par-

**Figure 2.** Apical four chamber view of transthoracic echocardiogram revealing severe dilation and hypokinesis of right ventricle with preserved left ventricular function; (top) diastole, (bottom) systole

infiltration with lymphocytes, eosinophils, plasma cells, macrophages and numerous multinucleated giant cells.\textsuperscript{1}

The pathogenesis of GCM is not well understood. Experimental animal models using autoimmunization against cardiac myosin in Lewis rats have replicated similar pathology.\textsuperscript{1} Evidence suggests that GCM is an autoimmune disorder dependent on CD4-positive T lymphocytes.\textsuperscript{1,3} This disease process frequently occurs in association with systemic diseases such

**Figure 3.** Hemodynamic tracings from cardiac catheterization demonstrating findings of left ventricular and right ventricular interdependence

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particularly true when associated with ventricular arrhythmias or heart block. The prognosis and treatment of Giant Cell myocarditis differ markedly from other myopathic disorders and require early, aggressive use of immunosuppressive therapy agents and evaluation for cardiac transplantation.

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Managing the Medication Portfolio and Avoiding Polypharmacy in the Older Adult

Ana C. Tuya, MD

Mrs. G is an 83-year-old woman whom you started seeing one month ago. Her previous medical records are still in transit from New York, following her move to RI in order to live near her daughter. She presented with a known history of chronic atrial fibrillation, managed on Coumadin and Digoxin; hypertension on Toprol, Diovan and Norvasc; reflux disease on Nexium; congestive heart failure on Lasix; insomnia on Trazadone; hypothyroidism on Synthroid; and depression on Zoloft. She also takes over the counter Tylenol as needed for osteoarthritis, Benadryl as needed, a daily multivitamin and Calcium with vitamin D. She is adjusting well to the move, likes being near her daughter, and enjoys her new apartment on the East Side of Providence. She remains very independent, only requiring transportation assistance to get to the store to do grocery shopping. You discuss wanting to make her medication regimen simpler, but decide to wait for records from her previous physician; she agrees and is to return to the office in one month. Two weeks later, after a record-breaking Rhode Island summer heat wave, you receive a panicked call from the patient’s daughter after finding her mother on the floor in her apartment confused and disoriented, and in a pool of urine. She is rushed to the Emergency department for evaluation.

Managing medications in the older adult becomes more complex; causes include 1) multiple underlying illness requiring intricate medications regimens, 2) multiple physicians – primary, specialist and sub-specialist - prescribing medications, and 3) frequent use of over the counter or herbal remedies. In addition to large numbers of concurrently used drugs, prescribing medications for older adults is challenging due to the changes in pharmaco-kinetics (how the body handles drugs) and -dynamics (how drugs affect the body) that occur with aging. Finally, older adults are not often included in clinical trials of medications; those that are included tend to be younger and healthier than typical elderly patients, often making use of some medications a non-evidence-based practice. Numerous adverse reactions and dose adjustments for older adults are learned through trial and error use of medications in the clinical setting.

The basic principles of pharmaco-kinetics are important to remember when prescribing medications to the older adult. To start with, drug absorption appears to be mostly unchanged with aging; however, disease states and other medications can affect absorption (atrophy gastritis, delayed gastric emptying, decreased splanchnic blood flow). Changes in drug distribution do have clinical importance in older adults. Absorption carries with it an increase in body fat content, a decrease in lean body mass, a decrease in total body water and a small decline in albumin concentration. Fat-soluble drugs will, therefore, have a larger volume of distribution, and water-soluble drugs will have a smaller volume of distribution. Drugs that bind to albumin may have less binding sites available, putting older adults at higher risk of toxicity from increased active drug concentrations; Dilantin is a common example. These factors combine to produce higher blood levels, earlier and more frequent occurrence of side effects and greater clinical impact at lower concentrations in older adults given standard doses of most drugs. Time to reach steady state is often prolonged several-fold. Accordingly, a geriatrics dictum when starting any new medication is “start low and go slow.”

Changes in renal clearance and hepatic function occur naturally with aging (the pure aging syndrome); common diseases and co-morbidities that increase in incidence with aging exacerbate these modest decrements. A gradual decline in glomerular filtration rate is seen in about 70% of the population, although there is variation in the degree of the decline from person to person; about 20% of persons seem not to show a decline in renal function with pure aging, and a smaller percentage (5-10%) show accelerated decline due to renal disease. On average, the decline is 1ml/min/yr after the age of 40. With the concomitant decline in creatinine production, serum creatinine is unchanged. For this reason, creatinine clearance should always be calculated and medications should be dosed accordingly; normal renal function should not be assumed based on a normal serum creatinine. Said another way, serum creatinine and BUN overestimate renal function in older persons because of decreased creatinine production in the first case, and decreased protein ingestion in the other. Both arise from decline in lean body mass with age. In the liver, the metabolism of medications, especially via phase I reactions (cytochrome-mediated) is delayed, leading to plasma and tissue concentrations that are usually increased. Dose reduction is generally required for hepatically metabolized medications.

Polypharmacy is a commonly discussed topic among practitioners who care for older adults. It is common for older adults to be on at least three daily medications, and many are on more. The risk of adverse drug reactions increases with the number of medications taken, and occur twice as often in older adults. In addition to the above physiologic changes that make medication use complex, drug-drug and drug-disease inter-
actions are commonly responsible for adverse drug effects. Polypharmacy can develop easily in the face of multiple practitioners prescribing for the same patient, old prescriptions that are kept and used on occasion, use of over the counter medications, and the common phenomenon of new prescriptions to treat side effects of other drugs. Unidentified non-adherence (resulting from financial hardship, sensory deficits, cognitive impairment, difficulty swallowing, complex regimens) can often lead to the use of additional medications when unnecessary (e.g., the addition of a second or third antihypertensive agent, when the original one is not being taken regularly or correctly).

Drug-related problems commonly seen include delirium, hypotension, incontinence, falls, loss of appetite and nephrotoxicity from high drug levels. Furthermore, many drugs have increased adverse effects in older adults—for example, the increased risk of gastrointestinal bleeding and fluid retention with non-steroidal anti-inflammatory drugs. Mrs. G. described above, is a classic example of this phenomenon. What are the likely contributory causes to her crisis event? Most likely her picture is due to the summer heat wave, during which Mrs. G had increased insensible losses, exacerbated by age-related decrease in thirst perception and baseline elevated ADH levels. These led to a clinical picture of dehydration and hypovolemia, worsened by Lasix. Diovan and Digoxin in the setting of hypovolemia most likely led to electrolyte disturbances, bradycardia or conduction disturbances, and acute renal failure. Any of these toxicities or a combination is a plausible explanation for her confusion.

In addition, the development of incontinence in a previously continent woman can be described as transient incontinence. Transtient incontinence is often a manifestation of a problem in other organ systems—often acute illness or other stress. This was described in last month’s column as part of the concept of aging as a progressive restriction of the capacity to maintain homeostasis — “homeostenosis.” Homeostenosis, although a made up word, vividly describes how, in older adults, only modest severity of physical illness, drug toxicity or trauma often results in catastrophic declines, leading to a cascade of seemingly unrelated problems (pneumonia presenting with confusion, falling, urinary incontinence and loss of self-care capacity). One can expect that with resolution of her acute problems, the incontinence will also resolve.

In order to prevent such crises, laden with risk for irretrievable functional loss, it has become commonplace in many practices to request that patients “brown bag” their medications and supplements on the first, if not all visits to the practitioner. Reviewing in detail all medications, both over the counter and prescription will allow an accurate inventory of what the patient is taking. This review allows the practitioner to detect and prevent dangerous interactions or adverse effects. In addition, adherence can be assessed, as well as any reasons behind non-adherence. Finally, it is a good opportunity to review each medication for continued indication. If no reason for use is found, or if a medication is being used to treat the side effect of another, discontinuation should be pursued. When prescribing at any time in an older adult, consider cost, adherence and risk factors for non-adherence, and review current medications before adding new ones to look for potential interactions. For the most part, in older adults, less is more, and stopping a medication is usually a better option than adding one.

For example, our patient would have benefited from a streamlining of her medications; most glaring is the use of Benadryl in an older adult. Due to its strong anticholinergic effects, Benadryl is a relatively contraindicated medication in the elderly patient population. Classes or particular medications to be aware of are described in the Beers criteria, updated in 2003. A useful website was designed at Duke University that provides a quick reference link to a summary of drugs to avoid, and a web-link to the original article. The link is: http://www.dcri.duke.edu/ccge/curtis/beers.html. It is useful to review this list before choosing drugs of certain classes for use in the older adult. Many drugs that are benign in younger patients can lead to significant adverse reactions in the older patient.

In summary, medication profiles should be reviewed regularly, in detail, with older patients as a part of routine office care. Managing the medication regimen of a patient with multiple conditions is complicated, and many drugs are necessary; however, less is often more. Remembering the basic pharmacologic principles and the usual changes that occur with aging, as well as reviewing the common danger drugs for older adults will be a useful start in keeping an older adult’s medication list optimally beneficial and least likely to produce harm. It is important to critically question each and every medication. This practice will diminish the likelihood of one’s older patient presenting with adverse drug reactions and complications such as those demonstrated by Mrs. G.

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The organization of RI’s thirteen community hospitals as 501(c)(3) corporations enables them to carry out their charitable missions without the tax liabilities imposed on for-profit companies. The economic value of this “not-for-profit” designation is considerable, and the community, in waiving its right to these revenues, implicitly anticipates that it will benefit from the “public good” of certain benefits provided in return. Chief among these are healthcare services rendered to all patients regardless of their ability to pay (i.e., charity care).

Rhode Island was one of the first states in the nation to examine hospital community benefits. Since 1989, the RI Department of Health (HEALTH) has analyzed and reported on this issue. In 1997, the General Assembly passed the Hospital Conversions Act (the Act) that further codified the public reporting of these activities.

**METHODS**

The Act and its regulations broadly define community benefits as “…the provision of hospital services that meet the ongoing needs of the community for primary and emergency care,” and furthermore state that they “shall …not be limited to charity care and uncompensated care,” but include “programs …that meet the needs of the medically indigent,” “linkages with community partners,” “non-revenue producing services,” “public advocacy,” and “scientific, medical research, or educational activities.”

Notwithstanding the Act’s broad definition of community benefits, charity care remains the most fundamental measure of a hospital’s community benefits. Charity care is the charges recorded for services delivered but never billed because the hospital determined the patient was incapable of payment. A patient receiving charity care is means-tested and found to be medically indigent, or too impoverished to pay for their care.

Bad debt, on the other hand, is often cited as a community benefit but is, in fact, a normal, competitive business expense incurred by every business marketing goods or services. In this case, bad debt is the billing for healthcare services rendered to patients capable of payment, but never received and written off as uncollectible.

In order to quantify the hospitals’ efforts in providing community benefits, an annual survey, audited financial statements, and Medicare Cost Reports are used to collect descriptive and financial data. To allow for more valid comparisons between institutions and over time, the charity care charges reported by hospitals are cost-adjusted by applying yearly, hospital-specific ‘Rate Adjustment Factors’.
The Governor’s 2005 Wellness Initiative identified five goals to focus statewide public health improvement efforts: 1) reduce obesity, 2) reduce smoking, 3) increase consumption of fruits & vegetables, 4) increase exercise, and 5) increase seatbelt use. Table 1 summarizes each hospital’s own grouping of its 2005 support for these objectives, as well as for increasing healthcare access, unreimbursed graduate medical education (GME) expenses, and a final category for all other community benefits activities.

Regarding ‘Increasing Healthcare Access,’ $29.8 million or 89% was from direct charity care healthcare services to patients. With respect to ‘Reducing Obesity,’ $3.2 million or 94% was from unfunded research in this field. The ‘Other’ category includes such activities as community outreach, health screenings, patient education, health clinics, and patient transport/financial counseling.

Figure 1 provides the statewide charity care expenses and percentages from 2000 through 2005. Over this six-year period, the charity care expenses increased fairly consistently, from $14 to $30 million. In the highest year, 2005, the burden of this care was 1.3% of patient revenue statewide.

DISCUSSION
Since 1998, HEALTH has had formal data collection efforts to track and quantify hospital community benefits. As the debate over what constitutes a ‘charitable’ organization continues, policy makers struggle with the need for more and better information. In response, HEALTH has expanded its public reporting and revised the metrics used to frame and analyze the issue.

In addition, HEALTH uses this opportunity to align the hospitals’ community benefits activities with its own public health initiatives. Understandably, not every hospital addresses all of these areas, because each hospital’s priorities should reflect its own community needs, but it does serve to illustrate where the industry and the state may work together more effectively.

REFERENCES
1. Rehabilitation Hospital is a Limited Partnership, a wholly owned subsidiary of Landmark; its net income flows up to tax-exempt Landmark; and its financial statements are consolidated with Landmark’s.
3. These charity care expenses (and percentages) are reported without regard to the specialized revenue some hospitals receive to subsidize or otherwise offset the cost of that care: 1) Medicaid Disproportionate Share Hospital (DSH) payments, 2) Medicare DSH payments, and 3) restricted endowment income donated to fund healthcare for indigent patients.

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The past decade demonstrated increasingly broad-based support for the implementation of evidence-based guidelines in everyday clinical practice in order to improve the management of the leading causes of US morbidity and mortality.\(^1\)\(^2\) However, the adoption of Evidence Based Medicine (EBM) and other generally accepted “clinical best practices” (CBP) continues to lag behind at the community level.\(^3\)\(^4\) Public health agencies, healthcare quality improvement organizations, and medical educators share a stake in promoting these practices in order to improve population health. The anticipated benefits depend not only upon regular use by busy clinicians in community practices, but also upon teaching CBP to medical students during the preceptorial phase of their education.

One review of 67 studies found that a variety of factors relating to the physician, guidelines, health system or patients influence compliance with CBP.\(^5\) Use of a more insightful theoretical framework for understanding and changing physician behaviors could help to reduce the gap between knowledge and routine practice.

Social marketing entered the professional literature over 30 years ago and has been applied to many areas of consumer and professional health behaviors. Social marketing applies “commercial marketing technologies to the analysis, planning, execution and evaluation of programs designed to influence voluntary behavior” and improve personal welfare and society.\(^6\) Five basic principles distinguish social marketing from other behavioral change approaches: 1) marketing’s conceptual framework; 2) audience segmentation; 3) focus on the consumers’ desires and needs; 4) willingness to modify the product and 5) careful, continuous monitoring and revision.\(^7\) Social marketing has contributed to the understanding of medical education and may provide a useful framework for analyzing and changing other professional behaviors, such as the use (and teaching) of clinical best practices.

In order to explore and understand the gap between guidelines and actual practice, we undertook a pilot qualitative study, employing physician focus groups—often a useful tool for gathering preliminary data. The overall objective of the study was to guide future research by addressing the following questions:

- How do practicing physicians weigh the “pros” and “cons” of using CBP?
- How do CBP guidelines compete with other influences on physician behavior?
- Does a social marketing approach help inform CBP implementation?

Social marketing exposes the gap between CBP guidelines and everyday practice by focusing on the audience. Traditionally, science based medical applications (“products”) evolve from academic settings into community practice—often without full consideration of how they fit with the desires and needs of the “target audience” (practicing physicians). A social marketing based approach keys on the needs of the audience, and then redesigns the product (within scientific parameters) to achieve a better fit. This pilot project illustrates both the merits of the approach and the kinds of findings that could be obtained in a full study and used to improve physician adoption of CBP.

**METHODS**

The partners in this collaborative effort included the Rhode Island Department of Health, Quality Partners of Rhode Island and Qualidigm, Inc. (healthcare quality improvement organizations), the Office of Medical Faculty Affairs and the Department of Family Medicine at Brown Medical School and Policy Studies, Inc. a public health education and marketing firm. The focus groups used a specially-designed facility in a local shopping mall. One researcher served as group moderator; others observed through a one-way mirror.

Investigators recruited a total of twelve subjects for two focus groups using lists from the RI Chapter of the American College of Physicians, RI Community Health Centers and family practices in the state. The focus groups were segmented into salaried (institution-based) and non-salaried primary care physicians and balanced for gender and years of practice. Subjects received $150 to participate. Limited resources severely restricted the sample size and precluded conducting additional subsequent group sessions. However, the authors suggest that the results, although not generalizable, strongly indicate a research approach that lends itself to further study.

*The Guide to Clinical Preventive Services* contains rigorously-evaluated interventions to prevent common illnesses and conditions seen everyday by primary care providers throughout the US and Canada. Investigators focused on two guidelines: breast cancer screening and tobacco cessation. Breast cancer screening includes a mammography and/or clinical breast exam (CBE) every 1-2 years for women age 50-69. It suggests that there is insufficient evidence for CBE alone or for routine mammography among younger or older women. The Guide also recommends routine smoking prevention counseling for children, adolescents and adults in addition to cessation for all tobacco users, especially pregnant women and parents with children at home, including the use of nicotine replacement therapy (patch or gum). We anticipated that the challenges pertaining to the implementation and teaching of these particular guidelines would evoke a range of underlying issues, behaviors and barriers.
The moderator’s guide addressed the following areas:

- Perceived benefits to using and teaching CBP
- Current behavior compared to CBP guidelines on breast cancer screening and tobacco cessation;
- Challenges associated with implementing and teaching the guidelines; and
- Recommendations for overcoming the challenges.

For the purposes of the focus groups, the terms “best practices” and “clinical guidelines” were used interchangeably.

**RESULTS**

Physicians reported that CBP aids practice in several ways—helps physicians to stay updated, provides an overview of current research, improves patient care and alleviates several medical liability concerns. Some physicians prefer guidelines emanating from professional organizations; others prefer academic or governmental “experts” in the field. They all expressed concern about maintaining a rigorous science base. Subjects wanted CBP to contain:

- A concise overview of the scientific method used to develop the guidelines;
- Information on the impact that the recommended practice has on patient outcomes; and
- “Tiered” measurement to help them prioritize which practices to implement if they cannot implement all of them.

This last item seems particularly important. *The Guide to Clinical Preventive Services* contains 70 recommendations for routine screening, counseling, immunization and chemoprophylaxis in primary care practice—a daunting number of tasks for any profession.

Physicians also reported numerous barriers to implementing best practices. (Table 1)

- **Table 1: Barriers to implementation of best practices guidelines**

<table>
<thead>
<tr>
<th>Breast Cancer Screening</th>
<th>Smoking Cessation Counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of consensus on guidelines</td>
<td>Low success rate</td>
</tr>
<tr>
<td>Guidelines not linked to data on improved health outcomes</td>
<td>Time problems in a busy practice</td>
</tr>
<tr>
<td>Patient fails to follow through</td>
<td>Insurance reimbursement/coverage</td>
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<tr>
<td>Difficult coordination with specialists</td>
<td>Patient attitudes</td>
</tr>
<tr>
<td>Patient fears</td>
<td></td>
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<tr>
<td>Reimbursement not commensurate with how long it takes</td>
<td></td>
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<tr>
<td>Forgetfulness</td>
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</tbody>
</table>

Physicians also talked about ways to overcome barriers to implementing best practices. Their recommendations centered on the following areas:

- **Improved Office Support**: tools such as automated office reminders or a service that summarizes current wait times for getting mammograms at various sites.
- **Insurance coverage**: gaps between CBP requirements and insurance coverage—such as Zyban for smoking cessation.
- **Acknowledgment that guidelines alone don’t always dictate physicians’ decisions**: Other factors that affect decision-making include their schooling, experience, personal views, independent research, and the patient’s individual situation (family history, etc.).
- **Multi-faceted approach to changing patient behavior**: Physicians strongly supported smoking cessation but argued that sustained change in smoking behaviors requires community resources such as support groups, patient education, media campaigns, and legislation, such as cigarette tax increases and bans on smoking in public places.

Most physicians reported that they generally teach medical students and interns by modeling CBP with their patients but this sometimes slowed down the pace of practice and exacerbated some of their original concerns about routine implementation.

**Conclusions**

This pilot study offers several potential implications for strategies of developing, implementing and teaching CBP.

- Intervention strategies must vary depending on the health issue and the barriers confronting implementation of a particular clinical best practice.
- Operational and reimbursement issues must be acknowledged and addressed as part of any intervention strategy.
Guideline development and implementation could benefit from using a social marketing (consumer-oriented) approach.

Based on the results of this preliminary study, the investigators make the following recommendations for future research. Policy makers and medical educators can use a social marketing approach to improve provider behaviors regarding the routine use of clinical guidelines. Social marketing can also help redesign clinical guidelines overall—taking practitioner’s needs into account. By doing so, additional formative research could improve the fit between guidelines and clinical practice, hence reduce barriers to physician compliance and improve population health outcomes.

Finally, this study suggests that the use of informed medical trainees to help providers/preceptors keep up to date on the science and implementation of the latest clinical guidelines can be an effective strategy for improving both their clinical and preceptorial behavior. Given the small sample size, the authors anticipate conducting additional research to fully confirm these findings and design interventions to demonstrate the application of these recommendations.

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The Administrative Simplification provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) mandated the adoption of standard unique identifiers for health care providers. On January 23, 2004, the Centers for Medicare and Medicaid Services (CMS) published its Final Rule adopting the National Provider Identifier (NPI) as the HIPAA-mandated provider identifier. NPIs are designed to provide a unique identifying number for each health care provider, to be used for certain standard transactions, such as the submission of claims for reimbursement for the provision of health care services.

Under the 2004 Final Rule, every HIPAA-covered health care provider must obtain his or her own NPI, even if he or she uses a billing agent to prepare the covered transactions. Likewise, all health plans, including Medicare and Medicaid, must use the NPIs to identify health care providers in standard transactions. The deadline to implement the use of NPI in standard transactions is May 23, 2007. Thus, by mid-2007, the NPI will be the only permissible provider identifier in standard transactions by HIPAA-covered entities, replacing any other health plan-specific provider numbers that may currently be in use.2

Why implement a new number?
The implementation of one single provider identifier is one component in the establishment of national standards for electronic data exchange for all health care related transactions. Similar to other national industries that have moved toward promoting electronic commerce, national standards in the health care industry will make electronic data interchange a preferable alternative to paper processing. Physician’s offices will benefit from the administrative simplification of needing only one number when dealing with any health plan or insurance company in the United States including Medicare and Medicaid.

How do physicians obtain their NPI?
CMS has developed the National Plan and Provider Enumeration System (NPPES) to assign NPI numbers. Providers may obtain NPIs in the following ways:

- A paper application
- A web-based application
- An Electronic File Interchange (EFI) process that offers a bulk enumeration through which a health care provider or group of providers can have a particular organization apply for NPIs on their behalf.

Further information about each of these processes may be found on the NPPES Web site: https://nppes.cms.hhs.gov.

What is the difference between a Type 1 and Type 2 NPI?
Whether to apply for a Type 1 or Type 2 NPI has caused some confusion. Although physicians ultimately make the decision on how they want to be enumerated, in most cases individual practitioners should obtain a Type 1 NPI, while physicians in a group should also obtain a Type 2 NPI for the group.

Who needs to be given NPI information?
Once the physician or the group has obtained the NPI, the number must be provided to billing agents, clearinghouses and all health plans and insurance companies with whom the provider does business. Requirements as to how to communicate NPI information to these entities may vary. The health plan and insurance company web sites or provider representatives will be able to provide more detail.

Providers that use business associates or agents to conduct standard transactions on their behalf must require those business associates to use their NPIs appropriately for those transactions.

Rhode Island health plans are reporting that they have received only a fraction of the NPIs from local providers. Of the 7,000 NPIs currently issued in the state of Rhode Island, less than half that number has been reported to the local health plans.

What is the deadline to obtain an NPI and what are the implications if the deadline is missed?
As required by HIPAA, covered entities will require the NPI on all transactions after May 23, 2007. Small health plans must do so by May 23, 2008. Claims submitted after this date without an NPI may be rejected. Therefore to insure no disruption in cash flow or business operations, providers must obtain and communicate their NPIs in advance of the May 23rd deadline.

Part of the statutory obligation of Office of the Health Insurance Commissioner is to encourage fair treatment of health care providers. A single unique identifier is one step toward simplifying the administration of the health care system and reducing some administrative burden on physician offices. This Office strongly encourages the provider community comply with the Federal Final Rule and obtain and communicate its National Provider Identifier to all business partners well in advance of the deadline.

For more information about the OHIC please visit www.dbr.state.ri.us/health_insurance.html

REFERENCES
1. For the purposes of the NPI Rule, a “covered health care provider” means any health care provider, including any physician, who transmits any health information in electronic form in connection with a transaction covered by HIPAA. 45 C.F.R. §§ 160.103, 162.402.
2. The compliance date for all covered entities except small health plans is May 23, 2007; the compliance date for small health plans is one year later—May 23, 2008.

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The formulation of drug products has been monitored since the early 19th century. The United States Pharmacopoeia (USP) was developed in 1820 to set the "standards" for drug products. Over the last century, regulations were set in place to further monitor and evaluate the use of prescription medications. The Pure Food and Drug Act was responsible for the creation of the United States Food and Drug Administration (FDA) in 1938. Today the FDA governs the regulation, evaluation, and approval of drug products. The FDA, under the regulation of the Food, Drug, and Cosmetic Act (FDCA), is responsible for ensuring that prescription drug products are both safe and effective for use in the population.

When the FDA approves the drug product, the approval is solely for the studied indication, dosage, and patient population. Certain drug classes are more frequently used off-label than other drug products. Some of these drug classes include anticonvulsants, antipsychotics, antihistamines, antiasthmatics, and cardiovascular agents. When reviewing prescribing trends for office-based physicians, approximately 21% of medications were prescribed for an off-label indication. When specifically reviewing drug usage in chemotherapy and pediatric patients, approximately 85% of medications are prescribed for an off-label indication. The regulations, legal and ethical aspects, and importance of off-label drug use are discussed below.

**Off-Label Drug Use**

Off-label drug use has been defined as the "use of a drug product outside the conditions specified within the FDA-approved product insert" and may include use of a drug at a lower or higher dose than recommended, in a population or age group that was not studied, for an indication that was not evaluated, or by a route of administration that differs from the package insert. The term off-label does not mean that the drug product is used inappropriately, but that tolerability, safety, and efficacy data are not available for that particular usage. New or off-label uses may arise directly from clinician observation or "therapeutic innovation".

Off-label drug use by clinicians is permitted because of "medicine exemption," which states that "a physician may lawfully vary the conditions of use from those approved in the package insert without informing or receiving approval from the FDA." Additionally, the FDCA does not limit how a clinician may use an approved drug. "Medicine exemption" lets a clinician prescribe medication for what is considered an appropriate use without worry of legal ramifications. However, a clinician must use evidence and/or practice experience when prescribing outside the product labeling.

When evaluating the use of medication for an off-label indication, published information may be limited. As clinicians observe unapproved uses of medications it is important to report the drug use experiences, thereby allowing clinical information on the subject to be disseminated to other healthcare practitioners. In addition to the primary literature, resources that contain off-label uses of medications include the American Hospital Formulary Service-Drug Information (AHFS-DI), United States Pharmacopoeia-Drug Information (USP-DI), DRUGDEX® drug information system, and others. A standard of practice in off-label drug prescribing includes the use of these references as reputable sources of clinical, off-label drug use information. Some insurers base reimbursement on whether or not an off-label drug use is found in either the AHFS-DI or USP-DI compendia. Insurers consider items included in these drug compendia as "approved" off-label uses (approved because it is found within these texts, not approved by the FDA).

In 1997, the FDA Modernization Act (FDAMA) changed the way the pharmaceutical industry could promote the off-label use of a drug, allowing manufacturers to use published peer-reviewed articles and reference textbooks in discussions of off-label drug uses with healthcare providers. If a pharmaceutical company initiates the process and provides off-label information to clinicians, the pharmaceutical company must submit the information that was provided, and to whom it was provided, to the FDA. The off-label use presented in the articles should be regarding a new indication that the manufacturer plans to submit in a supplemental application to the FDA within the next 36 months. Companies are exempt from submitting the application if the cost of performing studies on the new indication is more expensive than the expected monetary returns from the newly approved indication.

Professional organizations have established their own policies regarding the off-label use of medications. The two leading professional pharmacy organizations, American Pharmacists Association (APhA) and the American Society of Health System Pharmacists (ASHP), both support off-label drug use. ASHP’s position is, “freedom and responsibility to make drug therapy decisions consistent with a patient’s needs are fundamental”. They also support the responsibilities of a pharmacist to provide drug information and clinical practice standards regarding off-label drug use. The position statement and policies of APhA state that a collaboration should be formed between the pharmacist and other healthcare providers to evaluate off-label information and the organization also supports reimbursement by third party payers for therapies used off-label. The American Medical Association (AMA) takes the same stance as the pharmacy organizations in addition to unrestricted prescribing by a provider, regardless of approved or off-label use.
LEGAL AND ETHICAL CONSIDERATIONS

Physicians who prescribe medications for off-label drug use are not at risk for allegations of negligence or malpractice if decisions are based on clinical evidence and are consistent with community practice. An off-label indication for a medication may be the standard of care for a particular disease state. Therefore, it is important that a provider does not limit prescribing to FDA-approved uses because there may be instances where an off-label product is the best treatment option.

Off-label drug usage is frequently seen in special populations including children and pregnant women because clinical trials are not routinely conducted in these populations. Few trials are conducted in pediatric patients because informed consent needs to be obtained from the guardian of children less than 16 years old. Also, there is no financial incentive for pharmaceutical companies to perform trials in the limited pediatric population (i.e., the companies will not have a monetary return that will cover the costs of the clinical trial). Trials are not performed in pregnant women due to the potential for teratogenic effects in the fetus. Since off-label uses are not evaluated, it is not known what safety problems may arise from off-label use, especially in pregnant women. The thalidomide tragedy is a reminder of the importance of drug use evaluation in these sensitive populations.

The vast majority of medications used in the pediatric population are prescribed off-label because clinical trial information is lacking. An additional component of the FDAMA is an incentive for pharmaceutical manufacturers to perform clinical trials in the pediatric population. The FDAMA offers a 6-month patent extension to a pharmaceutical company that will perform clinical trials in the pediatric population. Companies receive patent extensions regardless of whether or not the pediatric information actually gets approved by the FDA for inclusion in the approved product labeling.

An additional ethical concern arising from off-label drug use is reimbursement from third party payers. Some managed care organizations may deny coverage for off-label indications because they consider the use investigational or experimental. Many state insurance programs, such as Medicaid, deny payment for drugs used off-label. Denial occurs even though the off-label drug use may be deemed appropriate. Some states may pay for the medication if the off-label indication is listed in a recognized drug reference as mentioned earlier, AHFS-DI or USP-DI. A population where this is a concern is in patients undergoing cancer chemotherapy. Government programs, Medicare and Medicaid, are required to cover "medically appropriate" chemotherapy. These programs use the compendia system to determine if a use is medically appropriate, meaning that the indication must be listed in either AHFS-DI or USP-DI. However, there are no coverage regulations for private health insurance companies. A private health insurer, such as an Employee Retirement Income Security Act (ERISA) health plan, which is self-funded, is not required to cover off-label drug uses, even for chemotherapy. A concern surrounding the denial of payment is that patients may receive suboptimal care, especially if the off-label medication is frequently used for the particular indication in clinical practice. This concern is especially true when treating cancer patients with chemotherapeutic agents that have many indications for use, some of which may not be in the product labeling. In such instances, a patient would have to "pay out of pocket" for the clinically preferred regimen.

SAFETY

The adverse events for approved or "labeled" uses are found in the package insert and result from observations made during clinical and post-marketing trials. When using a drug product off-label there are concerns relating to patient safety and cost to the healthcare system. A greater risk of adverse effects is anticipated when medications are used off-label. The theoretical increase in risk results from a lack of information about the off-label use in medical literature and that medications that may be used in a particular population or at a different dose for the first time. An example that epitomizes the unknown risks when medications are used off-label is the controversy surrounding "fen-phen." As a treatment for obesity, fenfluramine and phentermine were combined. Both were FDA-approved for short-term use in the treatment of obesity; however, combined use and the longer treatment duration represented an off-label use which resulted in cardiac valve damage in some patients. Clinicians should inform patients who are using medications off-label of the anticipated adverse effects seen with the labeled use of a drug product. This may not be possible in the provider's practice setting and a pharmacist's services can be utilized to ensure the patient is aware of risks associated with the medication. If an adverse event arises from off-label drug use, it is important to report it to the FDA (via Medwatch) as well as the manufacturer to further establish the adverse effect profile of the medication.

IMPORTANCE OF OFF-LABEL DRUG USE

The clinician plays an important role in discovering off-label indications and reporting observations. The majority of new indications discovered for approved drug products are made by practicing clinicians, rather than researchers involved in the initial drug development. A review evaluated the quantity and initial discovery of new therapeutic uses for approved drug products. Of the new indications, with applications for labeling inclusion submitted to the FDA, approximately 57% were discovered by clinicians practicing in the field. This reiterates the importance of continued drug development and evaluation for innovative therapeutic indications.

Discovering new uses for approved drug products, especially in instances where there are limited treatment options, is necessary. Innovation is also important in those populations that frequently receive medication off-label, including pediatric patients, cancer patients, and human immunodeficiency virus (HIV) patients. Patients may want access to new treatments as soon as possible, rather than wait for a drug to un-
dergo extensive clinical testing. Investigations into off-label drug usage will continue to advance drug utilization. It is important to publish experiences with off-label drug use to enhance the literature available for peers to review.

CONCLUSION
Off-label prescription drug use is important for the advancement of pharmacotherapeutic treatment options. The identification of additional uses of a medication may encourage further studies of the drug product and/or disease state. The use of medications is not without risk; however, the more off-label information that is available to a clinician, the more likely the medication can be used safely in patients. Continued evaluation of drug products in the future will only improve patient care, especially in those populations with limited therapeutic options.

REFERENCES

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Prefixes play an important role in defining words used in a medical context. As they narrow the meaning of the root, they add character, direction and magnitude to the words to which they are appended. Prefixes may begin with any letter of the alphabet from “a” [anti-] to “z” [zymo-] but for no apparent reason a great plurality of them begin with the letter “p”; and most of these are of Greek origin.

Consider the prefix, poly-, [Greek, meaning, much or many]: English words with this prefix include such terms as polygraph, polymer, polymorph, polydactyl, polymath and polygamy [and its male-oriented partner, polyandry.]

The Greek prefix, phren-, sometimes refers to the diaphragm, sometimes to the heart, but usually to the brain. It appears in such medical terms as phrenitis [an older word for encephalitis], phenology [the pseudoscience of interpreting a person's character by studying the contour and bumps of his head], schizophrenia, phrenetic [sometimes spelled, frenetic] and frantic, originally meaning delirious.

The Greek prefix, phen-, means derived from or pertaining to and is found in both common words such as pheno-copy, phenobarbital and phenomenon and obscure words such as phenomenology [the study of the environment] and phenacetin.

Philo-, a Greek prefix meaning love of, may also serve as a suffix [as in Anglophile]. It is part of such words as philosophy, philanderer, philanthropist and syphilis [literally, a lover of pigs. The 16th Century Italian physician-poet Girolamo Fracastoro, wrote a poem about a shepherd named Syphilis, who ultimately was victim of what the poet called de morbo Gallico, the French disease [an earlier description of syphilis.]

The Greek prefix, pan- or panto-, meaning all, appears in words such as panacea [universal remedy], pandemic, pancreas [literally, all flesh], panegyric, pantheon, pantomime [literally, all imitating] and pantothenate.

Para-, a Greek prefix meaning beside, contrary to or abnormal, begins such words as paracentesis [to pierce at the side], parachute [that which protects from falling], paradox [contrary to beliefs], paragraph, parallel and paranoia. The word, parasite, means a pathologic organism, literally a guest who eats food. The Greek root, sitos, meaning food is seen in obscure words such as sitotoxin (continued on page 60)
Beyond a Signature
Informed Consent

John Tickner, CPCU, President, Babcock & Helliwell

Malpractice claims often result from a discrepancy between the patient’s expectations and the outcome of treatment. For years, doctors have relied on an informed consent form to protect them from legal recourse by a dissatisfied patient. However, in today’s legal climate, a physician must go beyond simply asking a patient to sign a form. Patients expect and courts require that informed consent be a process during which information is presented to patients to allow them to voluntarily decide on a treatment plan.

You must take the time to explain diagnoses, treatments, expected outcomes, potential risks, and your patients’ rights. To avoid omissions and insure consistency, you should develop your own informed-consent process. According to the AMA, doctors should disclose and discuss:

- The patient’s diagnosis, if known;
- The nature, purpose, risks, and benefits of a proposed treatment or procedure;
- The risks and benefits of the alternative treatment (regardless of their cost or the extent to which they’re covered by insurance);
- The risks and benefits of not receiving or undergoing a treatment or procedure.

Experts in the field recommend that you use medically correct wording and names, but avoid medical terminology. If possible, give the patient reading material about the treatment to take home.

The patient should be encouraged to ask questions. This helps determine if he or she understands the treatment or procedure and it shifts the decision-making responsibility from the doctor alone to a mutual doctor-patient responsibility.

A patient who rejects a proposed treatment after a full disclosure is then responsible for treatment outcomes. In addition, to protect yourself from future litigation, you must document the communication process. Good documentation can serve as evidence that the process took place. Follow these steps for a thorough informed consent process:

- Include the patient’s name, diagnosis, proposed treatment plan, alternatives, potential risks, complications, and benefits in the documentation.
- Include the name and relationship of any translator if the discussion took place in a language other than English.
- Include specific questions or concerns raised by the patient along with your answers.
- Document any materials explaining the procedure or treatment you gave to the patient.
- Include a statement to the effect that the information on the form is general, and that you have personally discussed specific factors with the patient. (This may protect you, to some extent.)

Have your attorney review any form that you use. A well-designed consent form can be useful, but an overly broad or highly detailed form can work against a doctor during litigation. If your form contains a list of possible complications or outcomes, your attorney will probably suggest that you insert language indicating that the list is not exclusive.

Having patients (or their legal guardians) sign and date a consent form serves to document the oral discussion and verify patient agreement and understanding. Any staff member can be authorized to obtain a patient’s signature, but you should sign or initial the form if you are present when the form is signed. As an additional risk-management measure, staff members should ask patients what treatment or procedure will be done and why before asking them to sign the form.

Keep the original form in the patient’s file and give him or her a copy to review at home with family members. Encourage the patient to call with any questions.

Following a thorough informed consent process will not completely eliminate claims, but it can help prevent a patient’s disappointment with treatment from turning into a claim.

John Tickner, CPCU, is president of Babcock & Helliwell, a privately held independent insurance agency established in 1892 that provides professional insurance-related services of all kinds. Babcock & Helliwell is an agency for ProMutual Group, New England’s largest medical malpractice insurance provider and the second-largest provider in Rhode Island.
Ninety Years Ago, February 1917

Lucius F.C. Garvin, MD, in “Prevention of Disease,” drew “a logical analogy between the human body and the body politic.” Specifically, he noted the value of “the public till” – a value that rose as land values rose, that a community could capture via taxation, to pay for roads, schools, etc. He urged a tax on “land value,” calling it “nature’s law for public revenue.”

Isaac Gerber, MD, in “Modern X-Ray Therapy,” praised the improvements over the “old-time coil,” with its weak electrical energy and an unstable output of x-rays. In particular he praised the Coolidge tube, the use of filters, and the adequate system of dosage.

An Editorial noted that “The Society for the Scientific Research and the Obliteration of Common Sense and Things Taught by Experience,” still exists. The Editorial told the tale of a man who was getting fat. “His story was soon told: a hearty breakfast, a ride to his office and close application to business for 10 hours, broken only by a few minutes for pie and milk, serving as a lunch, a hurry home for a big dinner with an antiprandial cocktail and then an evening spent either at the office, in committee or church work, or some of the inevitable banquets. Why was he getting fat? Why was he short of breath?” His physician ordered blood pressure tests, put him on a daily doses of medication: “He returned, now with real symptoms.” More tests (“a tracing of his pulse,” “a Wasserman”) followed, with more treatments. Eventually the patient truly was sick.

Fifty Years Ago, February 1957

In “Traumatic Neuromata of the Digital Nerves,” Stanley D. Simon, MD, and Carroll M. Silver, MD, described the technique they had used in 70 cases, with 2 failures.

Robert R. Baldridge, MD, President, Providence Medical Association, discussed “The Problem of the Foreign-Trained Physician.” There were 595 medical schools worldwide. From 1941-1950, 18 foreign-medical graduates took the exam; 16 passed. In 1955, 47 took the exam; 35 passed. Over the past five years RI had licensed 159 foreign medical graduates via the exam, 128 via reciprocity. Half will remain in RI to practice. States’ requirements varied. Dr. Baldridge observed: “The listing of acceptable foreign medical schools as a guide to state licensing bodies or to hospitals has been largely disregarded in this state and throughout the country.”

Edwin Dunlop, MD, Assistant Medical Director, Fuller Memorial Sanitarium, argued the benefits of the Funkenstein test of the autonomic nervous system in “Selectivity of Treatment in Psychiatric Patients: 500 Autonomic Nerve Reactions.”

An Editorial, “Atherosclerosis – The Price of Prosperity,” discussed the “number one killer,” noting the perils of “hard fat” ingestion: “…just as the diabetic can lengthen his life by diet and insulin, so the aging population of our country, by a bit of selective dieting…can extend the expectancy of life…”

Twenty-Five Years Ago, February 1982

Charles E. Millard, MD, President of the RI Medical Society, in “President’s Corner,” discussed “Cost Sharing is Terminological Legerdemain.” “Cost sharing and cost shifting are euphemisms which disguise the …fact that Medicare, Medicaid and Blue Cross do not pay full charges for hospital services in some cases, and in other cases do not pay any charges for services.” At Rhode Island Hospital, an estimated 4-5% of the $50 million in annual costs for Medicare patients was not reimbursed.

Kate Kiley MD, and L.R. Jenky, MD, in “Progress in Neurology: Electrocardiographic and Cardiac Enzyme Abnormalities in Acute Cerebrovascular Disease,” presented a brief review of the literature.

Mary Ann Passero, MD, Richard Frates, MD, and Don B. Singer, MD, contributed “Clinical Pathological Conference: Respiratory Distress and Severe Cyanosis in a Full Term Neonate.”

Peter P. Yu, MD, Deborah White, MD, and Edward A. Iannuccilli, MD, FACP in “The Mallory-Weiss Syndrome in the Pediatric Population,” urged physicians to consider this “rare condition … in the presence of hematemesis.”

Tom J. Wachtel, MD, in “Thyrotoxic Subacute Thyroiditis Associated with Hepatitis,” noted that the “pathological relationship between the disorders is not clear.”

Lexicon

(continued from page 58)

[food poison] and sitophobia [a fear of food.]

The Greek prefix, peri-, appears in common words such as perimeter, pericellular, periphery, pericardium, periorbital, peritonitis and perineum.

Plia- is a prefix of Latin origin [plicare, meaning to fold] and appears in English words such as plica, duplicate, pliers and pliable.

Less common Greek prefixes beginning with the letter “p” include parvi- [meaning small, in words such as parvicellular], phono- [meaning sound, as in telephone], photo-, meaning light, as in words such as photograph. And poikilo- [meaning varied or multicolored, in words such as poikilocytosis.

And then there are still other prefixes beginning with “p”: pneumo-, pleuro-, pseudo-, pachy-, pedo-, paleo-, papillo-, partho-, patho-, pecto-, pedi-, pene-, pento-, per-, picto-, pithec-, pisci-, plagio-, plano-, platin-, pluri-, pod-, pre-, post-, pro- and countless others.

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