Volume 94 No. 3 March 2011

Medicine & Health
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# Primary Care
# Part 1

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**Medicine & Health RHODE ISLAND**

VOLUME 94 NO. 3 March 2011

PUBLICATION OF THE RHODE ISLAND MEDICAL SOCIETY

## COMMENTARIES



## CONTRIBUTIONS

***Special Theme*: PRIMARY CARE – Part One**
***Guest Editor*: Yul Ejnes, MD, FACP**



## COLUMNS



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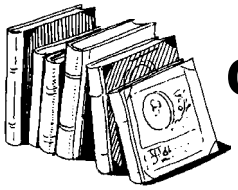

# Commentaries

## A New Paradigm for Clinical Studies?

**Most readers are not clinical trialists but** we are all affected by the results of clinical trials and are therefore interested parties in their design and logistics. Performing clinical trials is not easy, but how hard depends on where you are in the hierarchy. The foundation of any trial is, of course, an idea. Some are clever and reveal creativity and a deep understanding of a problem, but these are few and most are pretty straightforward, requiring little imaginative thought. For example, why not determine if drug X cures problem Y in a particular disease? A drug that works on one autoimmune disorder might work on another. Yet some drugs are not tested for obvious indications, and may be used liberally although there is no data to support its use. "It makes sense that if it works in population A it will work in population B" but only if A's ailments share some pathophysiologic substrate with B's problems.

In my niche, I regret to report that there have been no studies on the treatment of anxiety in **Parkinson's disease (PD)** although anxiety affects 25-40% of people with the illness and there is reason to question whether drugs that work in the general population will work in PD, which likely has a different pathophysiology. The reason for this lack of data is funding.

How do trials get funded? Most are sponsored by pharmaceutical companies that have a product to sell. This means we don't try to find out which is the "best" drug for treating a PD-related problem, only whether drug X produces significant benefit and is tolerated. Sometimes someone gets an idea to test a drug for a new indication. When the drug is under patent, the company may sponsor such a trial, partly to increase the drug's exposure, and partly to enhance the drugs' reputation, possibly even to have its benefits extended into "off label" uses, as was the case for gabapentin that sold more for off-label use than on. However, when a drug is not under patent, the potential funding is much harder to get. There are foundations which may sponsor treatment trials, but trials are enormously expensive, and the NIH is therefore left to sponsor most trials, usually at great expense. The foundations can't afford to fund many trials and tend to focus on basic research, which is where the cures or the preventions are going to be found, and which are much less expensive and faster at producing results.

To apply for an industry grant requires only a little effort and has a high rate of return. Since the usual applicants for grants are experts in the field who have clinical trial experience, it usually takes only a few-tens-of hours to put together a protocol and a budget, and the company usually responds fairly quickly, taking weeks to months. The NIH is a very different story, with grant applications taking hundreds of hours, often with many busy individuals involved, and no room for error or flexibility. The rate of return is miniscule. The rate of grants being funded varies with the Institute, but a figure as low as 3% is one that was quoted to me recently. This means that only the top 3% of applicants were funded. This is 3% of applications written by university professors with lots of experience, publications and established records. Most institutes fund a higher percentage, probably about 10%. This means that several people will spend hundreds of hours to no purpose. This translates into many people not bothering to "waste" their time by writing grants unlikely to be funded, regardless of their quality. Since the decisions to fund are based on multitudinous considerations, including how "important" or "novel" or "sexy" the proposal, non-sexy, non-novel, non-life-changing treatment trials may not be funded. Which brings us back to anxiety in PD, or apathy in PD or fatigue in PD.

My suggestion is only partly novel. I propose that funding institutes define clinically important problems and instead of putting out an "RFP" (request for proposals), put out a request for interested parties. From this group of interested parties, a handful of experts would be chosen to design a clinical trial and then choose the sites from the other interested applicants. The National Institute of Neurological Disease and Stroke currently has a project testing medications that might be protective for PD patients, that is, might slow disease progression. Estimating that only drugs with significant benefit are worth testing, only small numbers of subjects are required, and multiple drugs can be tested over relatively short periods of time. But there is no reason this concept cannot be extended to other treatments in every disease that has unmet needs, which is probably most diseases.

This approach to disease treatment is only partly competitive, in that interested parties would compete for participation, which will undoubtedly lead to the more famous, better established having a clear advantage over other interested parties. But to think that this is not already the case in the review process would be naïve. Certainly a clever idea might emerge in responses to RFP's that might not in a setting where the participants were chosen by their interest and track record. However, one can easily imagine a process in which, in addition to public solicitations for interested investigators, requests for ideas to study and skeletal outlines for proposals are made, and, judging by the responses, certain potential investigators could be invited to flesh out their proposals and possibly present them before review panels.

Our current approach may be the most efficient long-term, when money is available, but is undoubtedly not efficient when money is tight, since most potential investigators, perhaps those with the best ideas, choose not to participate because of the low yield.

**– Joseph H. Friedman, MD**

### Disclosure of Financial Interests

Joseph Friedman, MD, and spouse/significant other. Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers' Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001–2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.

# Poverty, Malnutrition and Worms

**The great American theologist and preacher, Jonathan Edwards** (1703–1758), once declared: "A little, wretched, despicable creature; a worm, a mere nothing and less than nothing; a vile insect that has risen up in contempt against the majesty of Heaven and earth." The condemnation seems a bit excessive; and perhaps would be more appropriate for the bubonic plague-carrying louse; certainly that lowly invertebrate creature, the earthworm, that earnestly feeds the robins in spring and aids the fisherman in his riparian pursuits, doesn't deserve the full homiletic wrath of the Reverend Edwards.

And yet, did the Reverend know something about lowly worms that his 18th Century audience failed to grasp? Did he know, for example, that by the 21st Century, well over a billion humans would be chronically afflicted, encumbered with enduring diseases caused by worms parasitizing their bodies?

There is a parasitic worm called *Ascaris lumbricoides*; and as its species name indicates it is remotely related to the ubiquitous but innocent earthworm. *Ascaris*, however, reaches lengths exceeding 12 inches and over the millennia has adapted itself to a precarious dwelling within the intestinal tracts of humans. To get there, however, the *Ascaris* worm begins its life cycle by its fertilized eggs—of microscopic dimension—surviving in top soil.

And how did these many *Ascaris* eggs get there? The Western world is so civilized that it refrains from public mention of the unspeakable act of defecation, but not civilized enough to provide private facilities called privies or toilets for about one-fourth of its global population. Accordingly, the great outdoors is the site for this quotidian biological function; and necessarily the topsoil of vast territories is intermixed with what is coyly called night-soil. It should be remembered that the living female *Ascaris* worm, safely dwelling in the small intestines of its victims, generates up to 250,000 eggs per day.

So the process begins with a vast measure of topsoil contaminated with fertile eggs capable of surviving for months particularly in the warmer soil of the tropics. Human contamination begins in an act as commonplace as a foot soiled with earth or a farming hand smudged with soil that may carry these eggs to the mouth. And once within the warmth of the intestines, the latent egg evolves into a small larva that then penetrates the intestinal wall, enters the blood stream to end in the lungs. The barely visible creature then is coughed up, typically at night, and inadvertently swallowed to re-enter the gastrointestinal system to dwell generally within the small intestines. There it grows rapidly by feeding upon the food stuffs within the intestines thus depriving its victim of necessary sustenance.

Most often the victim is a child in villages with neither bathroom facilities nor an abundance of high-protein foodstuffs. The child languishes both physically and intellectually, deprived of achieving his full capabilities by a brainless parasite.

The spectrum of other predatory worms is awesome. There are worms that sneak into the human body by penetrating the soles of bare feet causing profound anemia (hookworm); there are worms that attack the urinary bladder and liver, causing a major tropical disease called schistosomiasis; there are worms that invade the skeletal muscles (in an ailment called trichinosis); and other worms that contaminate the drinking water and ultimately end up as pain-producing dwellers of skeletal muscle (called dracunculiasis); there are worms that attack the eyes ultimately causing blindness (onchocerciasis or river blindness); and even worms that enter the brain developing cysts as harmful and mortal as brain tumors. The variety of pathologic, parasitic worms is extensive; so much so that there is a separate science called helminthology devoted solely to its understanding and perhaps eradication.

It is not likely that the subject of invasive worms will be a leading subject for discussion at tonight's family dinner in the suburbs of this nation. Clearly, it is a distasteful if not repellent subject.

Are these chronic diseases treatable? Eminently, yes. Are they, preventable? Also, yes. But as long as about one-fourth of humanity remains on intimate terms with abject poverty; as long as most of the impoverished have little familiarity with the most rudimentary of hygienic resources; and as long as illiteracy prevails in vast areas, the parasitic worms will continue their amity with humans. In the prophetic words of Keats, life deprived of life's bounty is little more than "darkness and worms, and shrouds, and sepulchers."

– Stanley M. Aronson, MD

*Stanley M. Aronson, MD is dean of medicine emeritus, Brown University.*

## Disclosure of Financial Interests

Stanley M. Aronson, MD, and spouse/significant other have no financial interests to disclose.

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# Giving Thought to Primary Care

*Yul Ejnes, MD*

**When I was asked to serve as guest editor for two issues of** *Medicine and Health Rhode Island* on Primary Care, I did not give much thought to the term "primary care." But as the manuscripts started coming in, it occurred to me that the articles have little to do with what I think of as "primary care." They are relevant to my daily work, but that is because as an internist I treat patients with heart disease, gastrointestinal disorders, renal failure, and a variety of other conditions. So where does the "primary care" come in?

First, let's be clear that there is no such specialty as "primary care." The term describes a set of functions that may be performed by a variety of specialists. The Institute of Medicine defines primary care as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community."[1] Typically, internists, family physicians, osteopathic physicians, and pediatricians play this role, but so can subspecialists such as nephrologists, endocrinologists, and HIV specialists (the term "principal care" is often used).

So, why dwell on the nomenclature? Physicians who provide primary care face the loss of their identities as specialists, and with that, risk being viewed with less respect by patients, colleagues, and most importantly, future doctors. I am not a "PCP." I am an internist who provides primary care to all of his patients. While I coordinate care and address patient needs that are outside of traditional internal medicine (such as basic orthopedic and mental health care), the majority of what I do is internal medicine.

With the above in mind, these two issues of *MHRI* were originally developed with the goal of updating readers on common problems that internists, family physicians, and osteopathic physicians treat every day. But they also illustrate the comprehensiveness and complexity of the care that these so-called "primary care physicians" provide.

For these issues, I asked each author to focus on three specific questions on a topic in their area of expertise instead of providing a general topic review or update. This format is borrowed from a successful one used at regional and national American College of Physician meetings called "Multiple Small Feedings of the Mind." I hope that you find this way of presenting information an effective one and encourage you to write down questions for future editions of this journal (assuming that the Editor judges this effort successful).

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### Disclosure of Financial Interests

The author and/or spouse/significant other has no financial interests to disclose.

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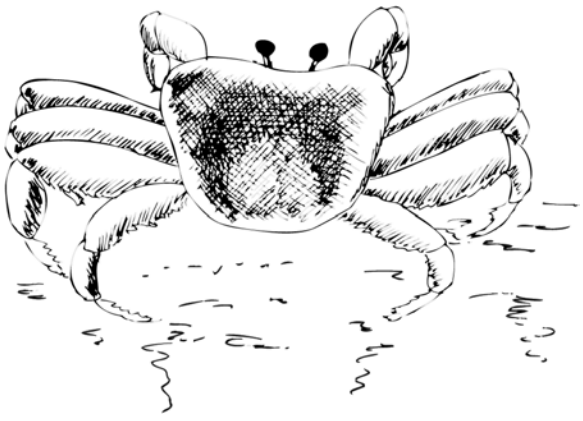

# Asymptomatic Elevations of Liver Enzymes: General Workup, Fatty Liver, Other Causes

*Thomas Sepe, MD*

**Asymptomatic elevations in liver function** are a very common problem in clinical practice. While dogmatic, the first rule is there is no such thing as a trivial elevation in the liver function tests. All such elevations require a working diagnosis and clinical follow-up.[1]

## How should elevated transaminases be worked up?

Elevated **liver function tests (LFT's)** can be sorted into disorders of cholestasis and disorders of hepatocellular injury. Cholestatic LFT's are characterized by an elevation predominantly in the alkaline phosphatase, while hepatocellular injury's hallmark is elevations in the AST and ALT. The practitioner, as with all clinical problems, must begin with a careful history, focusing on a detailed medication history, family history of liver disease (if any), alcohol intake, and risk factors for chronic viral hepatitis. The physical exam should focus on locating signs of chronic liver disease such as hepatomegaly, splenomegaly, ascites, edema, or spider angiomata. Finally, a directed laboratory evaluation should be undertaken including initial imaging of the liver and biliary tract when warranted.[2]

The person with clear signs of chronic liver disease should be referred immediately for subspecialty evaluation. Evidence for cholestasis should focus on medication toxicity, alcohol exposure, biliary tract disease, or the presence of primary biliary cirrhosis. The directed lab evaluation should include an antimitochondrial antibody and a right upper quadrant ultrasound. Evidence for hepatocellular injury should direct interest for medication toxicity, alcohol toxicity, hereditary hemochromatosis, fatty liver and/or **non-alcoholic steatohepatitis (NASH)**, or chronic **hepatitis B virus (HBV)** and **hepatitis C virus (HCV)** infection. Laboratory evaluation in this instance should include Fe/TIBC, HBsAg, HCV-Ab, and a right upper quadrant ultrasound. Ultrasound is favored as the initial screening tool vs. CT or MRI given its widespread availability, cost advantage and safety.

To lend perspective, the most common causes of asymptomatically elevated LFT's are medication or alcohol toxicity and fatty liver disease or NASH. If identified and corrected, medication or alcohol related elevations may not need referral and its associated costs, assuming the LFT's normalize with removal of the offending agent.

The diagnosis of alcoholic liver disease can be difficult given that most patients, at least initially, are reluctant to reveal an alcohol problem. The diagnosis should be suspected if the AST/ALT ratio is 2:1 or greater. In a classic study, an AST/ALT ratio greater than 2 had a 90 percent correlation with alcoholic liver disease.[3] This disorder is correctable assuming rehabilitation of alcohol abuse is accomplished, and the patient remains abstinent from further alcohol exposure.

Medications can cause minor and at times profound elevations in LFT's. While almost any medication has been reported to elevate liver function, common causes include statins, non-steroidal anti-inflammatory drugs, antiepileptic drugs, antibiotics, anabolic steroids and acetaminophen. Illicit drug use and herbal remedies should also be considered as causes of toxic hepatitis. Withdrawal of the offending agent will lead to resolution of toxicity, although it sometimes may take weeks and even months for complete recovery.[4]

## What is the recommended follow up and treatment of "fatty liver" (non-alcoholic steatohepatitis/NASH)?

The differentiation between fatty liver and NASH will need subspecialty evaluation and follow-up particularly given that NASH is a growing cause of chronic liver disease and is so common in the patient with metabolic syndrome.[5] The LFT's in fatty liver and NASH tend to be less than fourfold elevated. In contrast to alcohol injury, the AST/ALT ratio is less than one. NASH is more commonly seen in women, type 2 diabetes, and obesity. At the very least, exercise and weight reduction strategies—the only proven therapy at present—can be undertaken pending subspecialty evaluation. Non-invasive imaging such as ultrasound will show fatty infiltration approximately 65% of the time if present. (CT and MRI are more sensitive but more costly.) The diagnosis of NASH can only be made via liver biopsy. Only with histology can the distinction between fatty liver—fat-laden hepatocytes—and NASH—the presence of an inflammatory portal infiltrate (and risk for secondary fibrosis)—be made. Given limited medical therapies, liver biopsy is usually reserved for cases when the diagnosis is in doubt; for example, elevated iron studies in the setting of fatty liver.

Many trials are currently underway to develop medical therapy for NASH. There is growing data for Vitamin E supplementation as an effective adjunct in the care of these patients. The primary care physician plays a crucial role in these patients by tightly controlling diabetes and any lipid abnormalities if present. Unless there is advanced cirrhosis, there should be no problem with medications that are metabolized in the liver. In the case of statins, with their own inherent ability to elevate liver function as a known and common side effect, the primary care physician should not hesitate to treat lipid disturbances aggressively. These patients require periodic regular LFT's to look for elevations above their baseline-elevated levels, as a sign of possible statin toxicity. For example, a patient with baseline LFT's of ALT=110 and AST=100 who develops an elevations in the 300 range on a statin can be presumed to be showing signs of statin related drug toxicity.

## Which other disorders of liver function must be identified in the primary care setting?

Hereditary hemochromatosis is the most common adult inherited disorder but if found early, can be treated ef-

fectively, thus preventing advanced liver disease and its complications. Screening should begin with a calculation of the iron saturation—serum iron/TIBC. A saturation greater than 45% warrants checking the serum ferritin. If iron overload is confirmed, subspecialty referral is warranted. Genetic testing and a liver biopsy can be pursued. Genetic testing has not replaced liver biopsy, given that some patients who are homozygous for the HFE mutation (c282Y) do not have hemochromatosis; similarly, others may have hereditary hemochromatosis with no HFE mutations. Therapeutic phlebotomy is the treatment of choice and is well tolerated in most patients.

Finally, chronic HBV and HCV infections are very common in the United States affecting over one million and four million patients respectively. Both disorders currently have effective therapies—suppression for HBV and viral eradication for HCV. For HBV infection, viral suppressive therapies such as tenofovir and entecavir are very effective inhibitors of HBV viral replication, and prevent progression of liver damage in many instances.

For HCV infection, the next several years will see the doubling of HCV cure rates, with the potential prevention of end stage liver disease. The major challenge in the case of HCV will be the identification of infected patients, given that only twenty five percent of the four million affected Americans have been identified. If this epidemic is to be controlled, the primary care physician will play the key role in identification of infected individuals for referral for antiviral therapy. If suspected, given a history of risk factors such as prior blood transfusion or parenteral drug use, the PCP can screen for HCV by ordering an HCV antibody test; if positive, infection can be confirmed by ordering a HCV viral RNA level with subsequent subspecialty referral.

In summary, all elevations of liver function need careful study and development of an appropriate differential diagnosis. The approach outlined will be effective in framing the work up of the most common causes of these elevations, correcting some, and diagnosing others that will require subspecialty input. If this approach does not lead to one of the more common diagnoses, subspecialty referral is warranted to exclude more unusual disorders of the liver, for example, autoimmune hepatitis, Wilson's Disease, and alpha-1 anti-trypsin deficiency, among others. Careful collaboration between the primary care physician and the subspecialist will ultimately lead to cost effective, positive patient outcomes.

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### Disclosure of Financial Interests


The author and/or spouse/significant received grant research support from Gilead Sciences, Roche/Genentech, Merck, Vertex, and Bristol-Myers Squibb.


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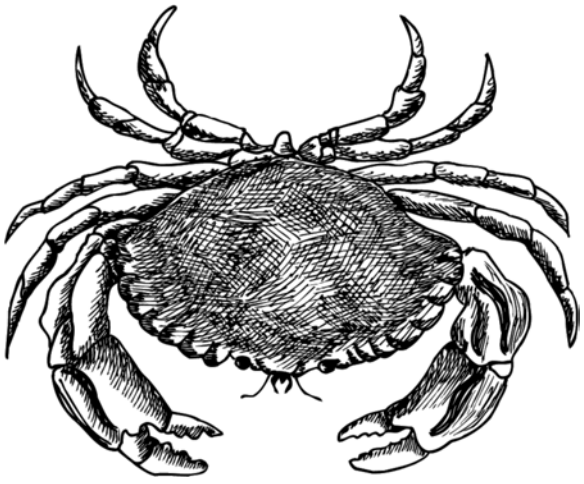

# Chronic Kidney Disease: Screening, Follow-up and Referral

*Mordecai Stolk, MD, and Charles McCoy, MD*

**The prevalence of chronic kidney disease (CKD)** and **End-stage renal disease (ESRD)** in the United States has been increasing.[1] There are more than one million people with stage 4 and 5 CKD and possibly as many as 20 million with stage 2 and 3 CKD in the United States. Evidence has been accumulating for decades that early detection and treatment of patients with CKD leads to better patient outcomes. In addition, it is believed that patients with CKD are at higher risk for cardiovascular disease. Far more people with CKD will die from cardiovascular disease than will develop ESRD. We will, therefore, attempt to answer three questions of relevance to primary care physicians caring for patients with CKD.

## Which patients should be screened for kidney disease and what are the best screening tests?

There is no clinical utility to the measurement of serum creatinine other than estimating the **glomerular filtration rate (GFR)**. There are other methods to measure GFR but these methods are either too cumbersome or costly to use as screening tests. The Cockcroft-Gault equation[2] typically overestimates true GFR. In response, a National Institutes of Health-sponsored study, the **Modification of Diet in Renal Disease (MDRD)**, produced a new equation to estimate kidney function.[3] Interest in this equation was galvanized in 2002 with the publication of a classification of staging CKD by the National Kidney Foundation and the **Kidney Disease Outcomes Quality Initiative (KDOQI)** based upon the **estimated GFR (eGFR)** derived from the MDRD (Table 1).[4]

Critics of the MDRD equation have cited problems with imprecision and bias. The most clinically relevant problem with the MDRD is that it systematically underestimates "true" GFR in subjects with GFR's greater than 60ml/min/1.73m2.[5] This underestimation of GFR improves as kidney function decreases but still remains unacceptably high at a GFR range of 30-59ml/min/1.73m2.[6]

Providing early intervention and curtailing the progression to end stage renal disease is the intention behind screening for CKD in a healthy population. However, it is not entirely clear whether universal screening for CKD is more appropriate than targeted screening. Proponents of universal screening believe that because CKD is essentially asymptomatic in the early stages, implementing preventative measures early in the course of CKD can retard progression of disease. Universal reporting of eGFR with the creatinine measurement could improve recognition of CKD. This line of reasoning assumes that physicians may have difficulty inferring GFR from a serum creatinine given its nonlinear relationship to GFR thereby creating an unnecessary delay in diagnosis.[7] Additionally, all of the equations used to estimate GFR are too complex to be used routinely in a physician's busy office schedule. Opponents of universal screening state that it would be expensive, create unnecessary referrals to nephrologists, engender pharmaceutical manipulation, and, most importantly, could cause emotional and/or financial harm to patients falsely labelled as having CKD.

Screening for CKD is believed to be beneficial to identifying patients at elevated risk of cardiovascular disease. Although many observational studies have identified CKD as a risk factor for cardiovascular disease, these epidemiological studies are limited by their inherent inability to establish cause and effect or adjust for confounders such as proteinuria or other comorbidities. For instance, the **Prevention of Renal and Vascular Endstage Disease (PREVEND)** trial showed that cardiovascular events did not increase in normo-albuminuric subjects as eGFR decreased from stage 1 to 3 CKD.[8] Another study with over a million subjects reported that the hazard ratio for a cardiovascular event occurred 20% more often in subjects with an eGFR of 45 to 59ml/min/1.73m2 compared to subjects with an eGFR greater than 60ml/min/1.73m2 after adjusting for many factors including proteinuria. This increased hazard ratio was lost when adjustments for co-morbidities were taken into account. However, there was a significant increase in both all cause mortality and cardiovascular events in subjects with an eGFR less than 45ml/min/1.73m2.[9]

The issue of albuminuria in relation to and being a requirement to diagnosing CKD is relevant. Not only is albuminuria

**Table 1. The Stages of Chronic Kidney Disease**

| Stage | Description | GFR (mL/min/1.73m$^2$) |
|---|---|---|
| | At increased risk | ≥ 90 (with CKD risk factors) |
| 1 | Kidney damage with normal or ↑ GFR | ≥ 90 |
| 2 | Kidney damage with mild ↓ GFR | 60-89 |
| 3 | Moderate ↓ GFR | 30-59 |
| 4 | Severe ↓ GFR | 15-29 |
| 5 | Kidney Failure | <15 (or dialysis) |

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m$^2$ for ≥ 3 months.
Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
*Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease.*

Adapted from: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 39:S1-S000, 2002 (suppl 1).

a sign of kidney disease, but it can also improve diagnostic screening accuracy. Albuminuria can be a sign of kidney disease and its presence is significantly associated with increasing all cause mortality, myocardial infarctions, and progression toward ESRD at each KDOQI stage.[10] At all levels of eGFR, the presence of dipstick positive proteinuria is associated with an approximately 100 fold higher risk of ESRD than subjects without proteinuria.[11] Additionally, the MRFIT study was a longitudinal trial of men at high risk for cardiovascular disease with 25 years of follow up. The positive predictive value of patients with an eGFR of less than 60ml/min/1.73m2 without proteinuria developing ESRD was only 5.6%. However, the positive predictive value increased to 26% with the presence of both a eGFR of less than 60ml/min/1.73m2 and greater than 1+ proteinuria.[12] Lastly, the authors of a large population based study of over 65,000 patients followed for over 10 years were able to demonstrate that both eGFR and albuminuria were independently associated with progression of CKD to ESRD, and referral based on both urinary microalbumin to creatinine ratio and eGFR could improve discrimination without losing predictive power to detect patients at risk of progressing to ESRD.[13]

Given all of the literature devoted to other screening tests such as cystatin C, the best screening test remains a serum creatinine. The test is cost effective, and when used with a validated equation for eGFR such as the MDRD equation has acceptable sensitivity and specificity to decipher who may or may not have CKD. Lastly, the diagnostic accuracy of screening for CKD with a serum creatinine can be increased by either adding an urinary microalbumin to creatinine ratio or using it in the context of the patient's other co-morbid conditions.

## How should patients with early stage chronic kidney disease be followed and treated?

Recommendations for patients with stage 2 and 3 CKD are complicated by the knowledge that only a small number of these patients will ever progress to ESRD. It is generally accepted that patients with hypertension, diabetes, or other diseases predisposing a patient to the development and progression of CKD should be screened yearly with a creatinine level and urinalysis. The frequency of screening healthy individuals including the elderly is controversial, but a creatinine and urine analysis should be done with any periodic examination and any hospitalization.

Patients with a eGFR >60ml/min/1.73m2 and microalbuminuria or overt albuminuria should first be evaluated for the cause of the renal disease. Persistent albuminuria on repeat evaluations over at least three months will need at least further follow-up to assess for progression. Patients with diabetes should be treated with an inhibitor of the renin angiotensin system to prevent progression to overt nephropathy,[14,15] have good control of their diabetes with a goal HgbA1c of 6.5% or less,[16] and a blood pressure goal of 130/80mmHg.[17]

Stage 3 CKD poses the greatest dilemma. Patients with diabetes should be treated in a similar way as patients with an eGFR greater than 60ml/min/1.73m2. Hypertension should always be controlled with a goal of 130/80mmHg for all patients with CKD even though the majority of these patients will have a normal urinalysis. Multiple lines of evidence substantiate that inhibitors of the renin angiotensin system are superior to other antihypertensive medications in slowing the progression of CKD.[18,19]

The diagnosis and meaning of mild to moderate CKD in the elderly is even more difficult to establish. CKD stage 1 and 2 is usually based on evidence of kidney damage either through imaging or the presence of albuminuria rather than the reported eGFR since the MDRD equation has been proven to be unreliable when the eGFR is greater than 60ml/min/1.73m2. CKD stage 3 is potentially a flawed category as it labels a significant proportion of the healthy elderly over the age of 65 years of age as having kidney disease when in fact they do not. Approximately 38% of adults over the age of 70[1] have an eGFR of less than 60ml/min/1.73m2 by the MDRD. Whether this is due to normal age related changes in GFR or true CKD is a matter of debate. Because of advanced age or low body weight, many people labeled with stage 3 CKD do not have clinically significant renal disease. Often only time will differentiate patients with progressive disease from those with a benign course. Periodic (at least yearly) reevaluation of blood pressure and serum creatinine appears to be the most prudent course of action.

## When should a patient with chronic kidney disease be referred to a nephrologist?

Patients should be evaluated by a nephrologist if they have: 1) an eGFR less than 30ml/min/1.73m2 regardless of etiology, 2) eGFR greater than 45ml/min/1.73m2 with significant albuminuria or significant comorbid conditions, and 3) any eGFR in the presence of hematuria, abnormal renal imaging, or a strong family history of renal disease, 4) declining eGFR over a three to six month period of observation, and 5) CKD with uncontrolled hypertension or other complications. The KDOQI Work Group focused on improving two specific outcomes in CKD: reducing the progression of kidney failure and the progression of cardiovascular disease. As CKD progresses, interventions to prevent and treat comorbid conditions that contribute to cardiovascular disease including hypertension, anemia, mineral bone disorders, malnutrition, fluid retention, and electrolyte abnormalities make management more complicated and referral to a nephrologist may be necessary.

The KDOQI guidelines state the goals of care of patients with eGFR less than 60ml/min/1.73m2 are predicated upon diagnosis and treatment of both kidney and comorbid conditions, estimating GFR through laboratory measurement, slowing progression of kidney disease, and evaluating and treating complications.[23] Clinicians should not use the result of a serum creatinine as the only method to assess kidney function.[24] Diagnostic accuracy is limited when either the size/ethnicity of the patient and a timeframe of three months between eGFR is not used. The rationale was to scale eGFR to a standardized body surface area and exclude transient declines in kidney function and random variations due to laboratory error, diet, and hydration status. These are all pitfalls clinicians face when trying to decide whether or not to refer a patient to a nephrologist.

This point is most clearly elucidated in the elderly. There is a lack of precision to the MDRD formula which tends to underestimate true GFR, especially in the elderly. Multiple lines of epidemiological data show that the relative risk of death associated with worsening of eGFR is abrogated in the elderly.[25-27] This phenomenon was recently described[28] in a community cohort study of approximately one million

participants in which there was a relative 68% increase in nephrology consultations for CKD following automated eGFR reporting. Since elderly patients with CKD have a greater risk of cardiovascular death than ESRD[29] and accepted management of CKD did not change, referral to a nephrologist on the based on eGFR alone may not change the patient's outcome.

We must therefore challenge the development of a disease oriented model of health care and focus on a patient oriented approach to CKD. Additionally, we should remember that although there is a strong correlation between CKD and cardiovascular disease in general, the correlation between death and moderate reductions in eGFR in the elderly population is weaker. Most importantly, we also must realize that an elderly patient with an eGFR of 45ml/min/1.73m2 has a different risk profile and lower risk of progression to ESRD than a 30 year old patient with the same eGFR. Therefore, health care providers should take an individualized approach to referring to a nephrologist for CKD that centers upon the estimated likelihood of kidney disease progression. For CKD patients with eGFR less than 30ml/min/1.73m2, the decision to refer is much easier as the rate of complications of severe CKD including hypertension, anemia, and mineral bone disorders rises directly with a decreasing GFR.[24] The challenge for the medical community will be to successfully balance the proper identification and treatment of actual CKD while avoiding nephrology referrals for mislabeled CKD and its attendant costs to the health care system and patient well being.

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### Disclosure of Financial Interests

The authors and/or spouses/significant others have no financial interests to disclose.

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# Coronary Artery Disease:
## Stress Testing, Follow-up and Referral

*Daniel J. Levine, MD, FACC*

**Coronary artery disease remains a** leading health problem in the United States. It accounts for major morbidity and mortality among men and women. The **National Heart, Lung and Blood Institute (NHLBI)** reports that one in four deaths annually is directly caused by coronary artery disease.[1] How we diagnose and treat coronary artery disease is a common concern for primary care physicians. While this review will not address the social concerns that arise when normal aging is defined as "disease," it will address three common questions that arise in the course of routine practice. First, what form of functional testing, (imaging vs. non-imaging) should be used in patient assessment? Second, how do we follow patients with stable coronary artery disease? Third, when should patients be referred to a cardiology subspecialist?

### When should exercise testing with imaging (nuclear, echo) be used instead of exercise testing without imaging?

In 1929, Masters and Oppenheimer first reported on the clinical significance of **electrocardiogram (ECG)** change, specifically ST segment change with stress.[2] Modern stress testing was born. The goals of stress testing need to be considered in a general framework prior to discussion of the specific options available to the practitioner. Stress testing is of greatest utility in two major settings: first, in the initial risk assessment of patients suspected of suffering from ischemic chest pain, and second, in evaluating patients with known disease who have had a significant change in symptomatology. Additionally, there is a role for stress testing in the diagnosis of stable coronary heart disease as well as in understanding prognosis after treatment for an acute cardiac event.[3,4]

In thinking about atherosclerosis, it is critical to note that it is a progressive natural process that occurs in the course of normal aging. While the presence of atherosclerosis does increase risk of cardiac events, it is not the cause of myocardial infarction. This process is the result of plaque rupture and thrombus formation and is not well predicted by stress testing. (Even a high-risk stress test, in the setting of stable symptoms, imparts an annual risk of only 5%.) Thus, when we describe a stress test as being "positive" or "negative" we are not really describing whether or not atherosclerosis is present, but rather, if symptomatic patients are experiencing symptoms in relation to obstructive coronary artery disease. While there is prognostic information to be obtained regarding risk in relation to exercise duration, development of anginal symptoms—particularly at a low work load—blood pressure response to exercise, chronotropic response and extent of ECG change or size of perfusion defect, this data is frequently subsidiary to the primary question being asked: are the patients' symptoms the result of coronary heart disease?

Stress testing is best understood as a function of probability statistics. The pre test probability for the presence of coronary artery disease affects the interpretation of the result. While Masters observed that ST segment depression was associated with the presence of obstructive coronary artery disease, the sensitivity and specificity of this test have subsequently been further evaluated. If there is a low pretest probability (<25%), then an abnormal test does not change the result. Similarly, a normal test in a patient with high pretest probability needs to be interpreted with caution. Stress testing is most valuable in patients with intermediate (to high) risk, where an abnormal result is most likely to reflect a true positive result. ECG changes with physical stress are a derivative function. Flow limitation leads to oxygen debt, leads to metabolic change at a cellular level, leading to electrical change that can then be observed on a macroscopic level through ECG monitoring. ECG change with stress is not 100% sensitive or specific for detecting obstructive coronary disease. Factors beyond ischemia affect exercise ECG, including baseline abnormality on the surface ECG (ST segment abnormalities, **Wolff–Parkinson–White syndrome (WPW)** or **left bundle branch block (LBBB)** for example) and medication affect. This has lead to the development of additional techniques to improve our diagnostic accuracy.

Perfusion imaging was developed in an effort to improve the diagnostic accuracy of cardiac stress testing. Radiopharmaceuticals share the basic property that they are taken up in the myocardium in proportion to blood flow. Understanding that myocardial blood flow is a regional phenomenon serves as a background for understanding the role of this technique. At rest, even in the presence of obstructive coronary artery disease there should not be flow disparity. With stress, myocardial demand increases and flow may then increase disproportionately. Imaging agents can then "track" this flow. Flow disparity, a defect, will be evident with stress, and resolve with rest when flow deficit resolves. (Assuming there has been no prior damage. Fixed defects then reflect infarction, rather than ischemia.) It is important to keep this in mind when we try to sort through the benefits of choosing one form of stress testing modality over another. Perfusion imaging does improve sensitivity for detection of ischemia with the following caveats. Since we are comparing "relative" flow, there can be false positives in the setting of balanced defects. Since these images are processed, there are multiple areas where artifact can be introduced leading to "false" positive results. Currently used radiopharmaceuticals emit gamma rays. Error can be introduced throughout image processing as it relates to image counts, soft tissue attenuation, and background subtraction.

Stress echocardiography developed similarly to perfusion imaging to aid in the diagnosis of significant obstructive coronary artery disease. Understanding how stress echo is done serves as a basis for understanding how and why it might be preferable to perfusion imaging or to

treadmill stress testing alone. Recognizing the problems associated with false positive and false negative stress tests, and in an effort to avoid the risk and expense associated with radiopharmaceuticals, stress echocardiography looks specifically at wall motion both at rest and at peak stress. In patients without a prior myocardial infarction, wall motion should be normal at rest. With stress, myocardial ischemia leads to regional wall motion abnormality, specifically, hypokinesis, and, if the ischemia is severe enough akinesis or even dyskinesis of the region subtended by the obstructed artery. Hence, when added to the stress ECG alone, wall motion assessment improves both sensitivity and specificity for detection of ischemia. Stress echo avoids the need to administer radioactive agents and is therefore "easier" and "less expensive". Due to the fact that the myocardial function is directly visualized, certain imaging artifacts that plague perfusion imaging, such as overlying soft tissue or artifact due to processing affected by count ratios and background subtraction, are avoided. This is not to say that stress echocardiography does not have its own limitations. Images at peak stress must be obtained rapidly (given that ischemia is transient, the moment that stress is terminated, ischemia should begin to resolve). Imaging windows can be difficult to obtain. Echo is affected by respiratory pattern and to a certain extent by overlying soft tissue. Finally, interpretation of stress echoes can be quite challenging and requires an advanced degree of expertise that is not universally available.[5]

Beyond answering the question as to whether or not a patient's symptoms are related to the presence of obstructive coronary artery disease, a great deal of information can be obtained simply by having a patient walk on a treadmill. For this reason, it is almost always preferable to consider treadmill or cycle ergometry as the mode of stress. Patients with a normal functional capacity who are able to exercise into stage 4 of a Bruce protocol, (an exercise effort that is roughly equivalent to 10 metabolic equivalents) , have an excellent prognosis from a cardiac standpoint (<1% risk of cardiac event at one year). This is independent of whether or not additional imaging is performed. Equally true is that patients with poor functional capacity have a worse outcome whether or not imaging is added. Additional data to aid the clinician including blood pressure and heart rate response, time to development of symptoms, time to onset of ECG change are all obtained regardless of the modality. Furthermore, the extent of the physiologic stress will also strongly impact ability to detect ischemia. Sub maximal stress may not provoke ischemia. Sensitivity of all stress testing depends on generation of an adequate double product (peak systolic pressure x heart rate). Use of common medications such as antihypertensives or beta blockers might inhibit the ability of all modalities to detect ischemia. Consideration regarding the specific question being assessed will affect whether or not testing is being performed in the presence of current therapy.

**For patients who cannot exercise, stress testing can still be performed.**

Nuclear imaging provides additional assessment, beyond non-imaging treadmill stress testing. Gated imaging, when it can be performed, gives information regarding wall motion as well as estimated ejection fraction. (Ejection fraction less than 45% being an independent factor of increased risk.) Ventricular volumes, right ventricular size, lung uptake of tracer, and extra cardiac tracer uptake can all be seen. Incidental findings of malignancies have been made in the course of cardiac exams. So too, stress echo provides additional information regarding valve structures, chamber sizes, ejection fraction and regurgitant lesions. (Complete echocardiographic study, involving Doppler assessment of valvular lesions is no longer routinely done concomitantly with stress testing. Most labs perform either a complete resting study, or a more focused study in the setting of stress echo. Comprehensive resting exams are more time consuming and are not reimbursed if done at the same time as a stress study.)

For patients who cannot exercise, stress testing can still be performed. Pharmacologic agents "simulate" physiologic stress. For perfusion imaging, adenosine, or a newer more cardiospecific agent, regadenosine, is generally the stressor of choice. These agents, through direct stimulation of adenosine receptors cause coronary vasodilatation and a supraphysiologic increase in coronary blood flow. Radiopharmaceuticals injected at peak pharmacologic stress can then track flow and detect ischemia just as you would under physiologic stress. This technique has been shown to be extremely safe and able to detect ischemia with a great degree of sensitivity and specificity. Similarly, dobutamine has been used in stress echo. At supratherapeutic doses of this beta agonist, myocardial ischemia can be provoked. Occasionally atropine will need to be added to provide adequate stress. Safety as well as sensitivity and specificity of this technique are equally high.

When choosing between stress test options it is important to note that regardless of the chosen modality, the greater the degree of obstructive disease, and the more proximal the obstruction, the more likely it will be detected. Left main coronary artery disease, or a greater than 70% stenosis of a major epicardial vessel is likely to be detected by any of the available techniques. The greater the extent of obstructive disease, the greater the sensitivity to detect it.

Are there times when a stress test is contraindicated? Given that these tests are diagnostic rather than therapeutic, and that we follow the maxim to "do no harm", there are obvious times when all agree stress testing is to be avoided. Acute infarction and unstable angina are two such. Most experts agree that exercise testing in the setting of severe aortic stenosis should only be done with the greatest of caution. In the era of frequent myocardial revascularization and intervention, we generally advise *against* vigorous exercise and maximal stress testing within the first few weeks after revascularization (particularly with drug eluting stents). There is some disagreement among experts as to how soon patients can safely exercise post stenting. Most agree that earlier than two weeks is too soon and greater than four weeks is certainly safe.

In summary, when choosing which test to order physicians need to think about the question they are asking and the particular risk group into which the patient falls, before deciding on which test to order. Physicians need to determine

if the pretest probability is high enough to warrant a stress test at all. It is always preferable to have patients exercise, given the additional information that is derived. If the patient has an abnormal baseline ECG, or if they are unable to exercise on a treadmill due to other physical factors, then alternative stress testing modalities must be employed. Additionally, it is well recognized that stress testing in women has a lower diagnostic accuracy. Imaging, in addition to exercise improves diagnostic accuracy but at additional cost. Some authors have suggested, and I agree, that it is reasonable to begin with a treadmill stress alone in women if they have a normal resting ECG and an intermediate risk for **coronary artery disease (CAD)**. Good functional capacity without ECG change, a negative test, carries low risk and no further testing is required. In this approach we would anticipate that 1/3 of patients would require no additional testing. An abnormal test, without imaging, however, would require further assessment. In any case, patients with abnormal resting ECGs need additional imaging (perfusion or echocardiographic). Patients who cannot exercise need pharmacologic stress and then additional imaging.[6]

### How should patients with stable CAD, including history of myocardial infarction (MI), be followed, including the role of stress testing?

How then do we follow patients with coronary artery disease? Is there a role for "routine" stress testing? In patients with coronary artery disease, much like patients with any chronic condition, "following" patients involves pursuing strategies shown to reduce risk of future events. Risk reduction is not the same as risk elimination. Testing itself does not eliminate risk; nor does it *prevent* heart attack. Strategies for risk reduction are well known and they include smoking cessation, blood pressure control, control of blood sugar and cholesterol lowering (in appropriate high-risk groups, most notably patients with prior vascular events). "Routine" stress testing does not appear in the list of known effective strategies to reduce risk (nor does CT scanning, MRI and even percutaneous intervention). In following patients, beyond efforts to control risk factors, a history that defines activity level and seeks to elicit the presence or absence of signs and symptoms of unstable or progressive disease may be the clinician's single most important tool in long-term follow up.

### When should a patient with coronary artery disease be referred to a cardiologist?

Finally, in approaching a patient with chronic illness it is important to consider when to ask for consultation input. While it seems obvious to say that it is almost never wrong to ask for a second opinion when questions arise, particularly in a field that is out of one's area of special interest or ongoing expertise, there are times when a consultation is warranted. In the setting of an acute change in symptom pattern, where intervention is required to immediately affect outcome, consultation is indicated. But what about in the setting of managing chronic coronary artery disease in general, and in selecting a modality for stress testing in specific? The answer to the first question will depend on the clinician's experience, time and interest. Patient factors, too, will often drive a request for consultation. And there is a range of acceptable practice patterns that will inform that choice.

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#### Disclosure of Financial Interests

The author and/or spouse/significant other has no financial interests to disclose.



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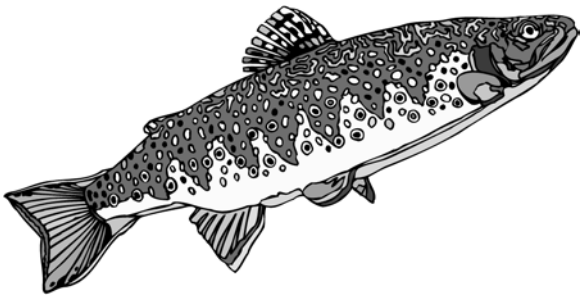

# Testosterone Deficiency in Men:
## Whom to Evaluate, What to Measure, and How to Treat

*Jennifer J. Miranda, MD, and Marc J. Laufgraben, MD, MBA*

### Whom should a primary care physician evaluate for testosterone deficiency?

Low testosterone levels in men are not uncommon. There is an age-related decline in testosterone levels, falling by about 1% each year.[1] Approximately 1% of healthy young men have total serum testosterone levels below 250 ng/dl and approximately 20% of healthy men over 60 years old have serum testosterone levels below 250 ng/dl.[1] However, despite the frequency of **testosterone deficiency (TD)**, especially in aging men, significant questions remain over whom to evaluate, what to measure and how to treat.

Men with TD commonly experience sexual symptoms such as loss of libido, erectile dysfunction, and decreased volume of ejaculate. More generalized symptoms such as lack of energy, loss of motivation, inability to concentrate, depressed mood, sleep disturbance, and irritability are also frequently seen. Patients may notice loss of muscle strength, muscular aches, hot flushes, and slow beard growth.

Sexual symptoms (low libido and erectile dysfunction) correlate best with low testosterone levels, with generalized symptoms being substantially less specific.[2] Unfortunately, even sexual symptoms have reduced specificity for TD due to the common occurrence of neurovascular causes of erectile dysfunction in aging men, as well as the many physical illnesses and psychosocial stresses that can result in low libido.

Physicians may also suspect TD if they note loss of body hair, very small or "shrinking" testes, height loss, or reduced muscle bulk.[3] TD should also be considered in men with certain clinical disorders where the prevalence of TD is high or for whom therapy may be recommended.[3] Such disorders include sellar mass or radiation to the sellar region; HIV-associated weight loss; end-stage renal disease and maintenance hemodialysis; osteoporosis or low-trauma fracture; moderate to severe COPD; infertility; and treatment with medications that affect testosterone production such as glucocorticoids or opioids.[3] TD is also very common in patients with type 2 diabetes.

It is important to note that self-report case-detection instruments such as the **Androgen Deficiency in Aging Males ( ADAM)** questionnaire have poor specificity and are not recommended.[4] Population-based screening in older men is also not recommended.

In summary, primary care physicians should pursue evaluation for TD in men with sexual symptoms or with disorders commonly associated with TD. Evaluation for TD can also be considered in men with more generalized symptoms.

### What tests should be measured in men suspected of TD?

The evaluation of men with suspected TD is made confusing by the inherent complexity of testosterone physiology as well as problems with assays to measure testosterone. Testosterone in men is secreted almost solely from the testes. About 40-50% of testosterone is tightly bound to **sex-hormone-binding globulin (SHBG)** and, as a result, is not accessible to receptors in target cells. Approximately 50-60% is loosely bound to albumin and the remaining 1-2% is in the free state.[5] The free testosterone and albumin-bound testosterone are felt to be "bioavailable," i.e. available to act on receptors in target tissues.

Because of alterations in SHBG and albumin (see below), measurements of total testosterone (which includes all free and bound testosterone), may not always accurately reflect the bioavailable component. Nevertheless, most studies of testosterone deficiency rely on measurements of total testosterone and, in general, commercial assays for total testosterone are felt to be much more reliable than assays for free testosterone.[6] Thus, measurement of total testosterone is the screening test of choice for patients with suspected TD. (Routine measurement of free and/or bioavailable testosterone is not recommended.) Testosterone levels demonstrate a circadian rhythm with the peak in the morning (though this circadian may be blunted in older patients).[7] Measurement of total testosterone should always take place in the morning (~8AM).

Although reported ranges for total testosterone are somewhat dependent on the specific lab and assay used, a total testosterone of greater than 320 ng/dl is considered normal.[8] Patients with a morning total testosterone greater than 320 ng/dl will not require further testing. Patients with lower total testosterone levels should have the test repeated in a few weeks to avoid the possibility of temporary low testosterone due to stress or illness. It has been reported that 30% of men may have a normal testosterone on repeat measurement.[3]

Men with total testosterone less than 200 ng/dl on more than one occasion have testosterone deficiency. Unfortunately, total testosterone levels in the range from 200-320 ng/dl are equivocal.[8] Such patients should have assessment of free or bioavailable testosterone. The gold standard for measurement of free testosterone is equilibrium dialysis, but this methodology is expensive and not widely available.[5] Fortunately, calculated free testosterone (using total testosterone, albumin, and SHBG) provides values nearly identical to free testosterone by equilibrium dialysis.[5]

Other than patients with equivocal (200-320 ng/dl) total testosterone levels, only patients suspected of harboring altered levels of SHBG should be screened with (calculated) free or bioavailable testosterone. SHBG levels can be altered in a number of circumstances including aging, obesity, diabetes, thyroid disease, and HIV.

The next step in the evaluation of hypogonadal men should be measurement of **lutenizing hormone (LH)** and **follicle-stimulating hormone (FSH)**. In the setting of low total testosterone, an elevated LH and FSH indicate primary testicular failure. In men with primary

testicular failure, karyotype testing to exclude Klinefelter's Syndrome should be considered.

Patients with low or normal LH and FSH in the setting of low testosterone have a pituitary and/or hypothalamic cause of hypogonadism (hypogonadotrophic hypogonadism). The optimal evaluation of such patients has not been determined. At minimum, a serum prolactin level (to exclude hyperprolactinemia) and iron saturation (to exclude hemochromatosis) should be performed. Patients with total testosterone levels less than 150 ng/dl have enhanced likelihood of abnormalities on pituitary MRI and pituitary function testing, and should be strongly considered for such evaluations.[9] Whether all other patients with hypogonadotrophic hypogonadism should undergo further testing of pituitary function is debated, but certainly should be considered if signs or symptoms of hypopituitarism are present. Similarly, any patient with hypogonadotrophic hypogonadism with signs or symptoms suggestive of mass effect from pituitary tumor (headache or visual deficits) should undergo pituitary MRI.

Because of the risk of bone loss, all men with testosterone deficiency should be considered for bone densitometry.

### How should patients with testosterone deficiency be treated and monitored?

Treatment for testosterone deficiency can be offered to symptomatic men with low testosterone levels with the goal of maintaining secondary sex characteristics and improving sexual function, sense of well-being, and bone mineral density,[3] provided that no contraindications to treatment exist. Testosterone therapy is not recommended for men with prostate or breast cancer, hematocrit above 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, or severe heart failure.[2] A **digital rectal exam (DRE)** as well as serum PSA measurement should be performed prior to the initiation of testosterone therapy. Men with palpable prostate abnormalities or a PSA > 4 ng/dl (or PSA > 3 in high-risk patients) should have further urologic evaluation before testosterone is considered.[3] Testosterone replacement is not the appropriate treatment for men with TD desiring fertility; such patients should be referred to endocrinologists or urologists for specialized evaluation and treatment.

Testosterone replacement is usually given by transdermal gel or patch, or by **intramuscular (IM)** injection. Testosterone gels are applied to nonscrotal skin once daily and are preferred by most patients. They are convenient, easily titratable and maintain steady day-to-day testosterone levels. However, gels are more expensive than other testosterone treatments. There is also the risk of potential transfer of testosterone to a sexual partner or child by direct skin-to-skin contact.

**Because of the risk of bone loss, all men with testosterone deficiency should be considered for bone densitometry.**

Testosterone patches are applied nightly to the hairless skin of the upper back, arm, or thigh; nightly application provides the closest approximation of the normal circadian rhythm of testosterone. Skin irritation and rash at the site of patch application is not rare; a low-dose triamcinolone cream applied prior to patch placement can reduce skin irritation without affecting testosterone absorption.[9]

IM testosterone was the major mode of testosterone treatment prior to the introduction of patches and gels. Intramuscular injections of testosterone enanthate or cypionate may be administered weekly (75-100 mg) or, more commonly, every 2 weeks (150-200 mg). With this formulation, the testosterone level peaks within a few days of administration and then slowly decline over the following 2 weeks. Its major drawback—in addition to the need for injection—is that men may develop fluctuating symptoms associated with the peaks (breast tenderness, hyperactivity) and valleys (fatigue, depression) of testosterone. Nevertheless, IM testosterone remains a common treatment for hypogonadism, particularly when cost is a factor or when men cannot achieve adequate serum levels with gels or patches.

Buccal tablets and implanted pellets are also available for testosterone therapy, but these are rarely used in routine practice. It should be noted emphatically that oral testosterone preparations are not approved for the treatment of testosterone deficiency in the United States and should not be used "off-label": they can cause serious liver toxicity.

The goal of replacement is to raise serum testosterone levels into the mid-normal range for healthy young men, roughly 400-700 ng/dl. In patients using gels, testosterone levels may be measured at any time of day. Patients using patches should have testosterone levels measured 3 to 12 hours after patch application.[3] Patients on IM testosterone should have testosterone levels checked at the midpoint between injections. Patients with levels above or below 400-700 ng/dl will require adjustments in their therapy.[3] Assessment of testosterone levels generally occurs after 3 months of treatment, but may occur as soon as 1-2 weeks after initiation of therapy in patients using gels.

In addition to being assessed for appropriate testosterone levels, patients require monitoring for potential adverse effects. A major concern is the potential for unmasking occult prostate cancer with testosterone replacement. Both DRE and PSA should be repeated at 3 to 6 months, and then in accordance with evidence-based guidelines for prostate cancer screening. If there is an increase in PSA > 1.4 ng/ml within a 12-month period of therapy, detection of a prostatic abnormality on DRE, or an AUA/IPSS > 19, then urologic consultation should be obtained. For those men who have sequential PSA measurements for a period more that 2 years, PSA velocity should be used for identification of men at higher risk for prostate cancer. If after 6 months of testosterone therapy the PSA velocity is > 0.4 ng/ml per year, then urological consultation is recommended. Men younger than age 40 are at low risk for the development of prostate cancer, and screening may not be necessary.[3]

Erythrocytosis, or hematocrit > 54%, can occur in testosterone replacement due to the stimulating effect of testosterone on erythropoiesis. Hematocrit should be checked prior to initiation of therapy, at 3 to 6 months, and then annually. Erythrocytosis results in increased blood viscosity, which increases the risk for vascular

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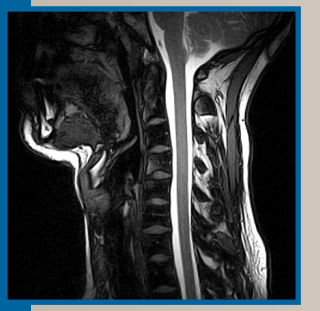

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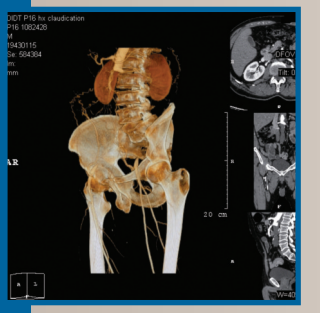

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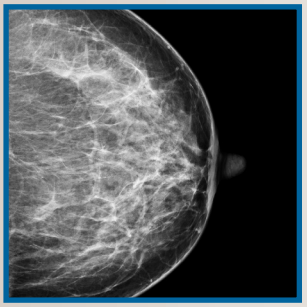

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events including stroke and myocardial infarction.[5] Transdermal testosterone is less likely to cause erythrocytosis than IM testosterone. If a patient is found to have erythrocytosis from testosterone replacement, reduction of dose, change in method of delivery, cessation of therapy or even phlebotomy may be indicated.

Development or exacerbation of sleep apnea may occur in patients otherwise at risk of this disorder. Gynecomastia may occur due to aromatization of testosterone to estradiol in peripheral fat tissue,[5] but is usually reversible if therapy is discontinued. Bone mineral density should be repeated after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture.[3]

The effects of testosterone replacement on cardiovascular health have not been determined. Recently, a trial of testosterone supplementation in older men with limited mobility was terminated early due to an increased occurrence of adverse cardiovascular events in the treatment group.[10] These results may have been due to chance. Still, the outcome should sound a note of caution.

It is important to recognize that recommendations regarding testosterone therapy are primarily based on short-term studies. The risks and benefits of long-term testosterone treatment are, unfortunately, unknown.

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The author and/or spouse/significant other has no financial interests to disclose.

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# Headache: Differentiating Among the Types, Use of Imaging, and Medication Overuse Headache

*Gary A. L'Europa MD, FASH*

### What clinical findings are most useful for differentiating among the various types of headaches?

When asked to comment on this topic I immediately thought of the advice that Seymour Diamond, founder of the Diamond Headache Center and the godfather of headache gave to his daughter Merl when she succeeded him as director, "Merl, it's all migraine." About 90% of all the patients that we see at The Headache Center are diagnosed with probable Medication Overuse Headache (Analgesic Rebound) on their first visit. Once they are successfully treated, their underlying headache disorder is usually migraine or a combination of migraine and tension type headache.

In a primary care setting, the vast majority of patients you will see with headache have migraine. As in all of medicine the history remains the key to diagnosis, however with primary headaches the history is the only means for diagnosis. There were no accepted ways to diagnose migraine until 1988 when The International Headache Society developed a classification of headache with criteria to diagnose each headache.[1] There are 14 categories that are divided into 3 groups: Primary, Secondary and Cranial Neuralgias. Primary headaches are those that exist independent from any other medical condition. Secondary headaches are those caused by another medical disorder. Even the members of the classification committee cannot remember all the criteria however in clinical practice it is helpful to know the criteria for migraine.

The diagnostic criteria for migraine are as follows:[2]

A. At least 5 attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:
   i. unilateral location
   ii. pulsating quality
   iii. moderate or severe pain intensity
   iv. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

D. During headache at least one of the following:
   i. nausea and/or vomiting
   ii. photophobia and phonophobia

E. Not attributed to another disorder

The most important item is A. The diagnosis of migraine should never be given to a patient experiencing their first migraine. Subarachnoid hemorrhage has mistakenly been diagnosed as migraine for this reason.

A three-question screening tool developed by Richard Lipton called ID Migraine® results in a predictive value of 93%.[3] The three questions were:

1. Has a headache limited your activities for a day or more in the last three months?
2. Are you nauseated or sick to your stomach when you have a headache?
3. Does light bother you when you have a headache?

Yes to any two results is a positive screen.

Although tension headache is the most common headache, patients seldom seek medical attention.

Cluster headache is considered the most severe headache pain. It is seen 18 times more commonly in men. The associated nasal congestion, eye tearing, and scleral injection result in its commonly being misdiagnosed as a sinus infection. The best clue is the shorter duration of the headache (cluster headaches almost never last longer than 3 hours even without treatment).

In my experience, the most common secondary headache is medication overuse followed by post-traumatic headache. If there is one diagnosis that I make sure we never miss, it is temporal arteritis. This headache is seen almost exclusively in patients over 50 years old. Although temporal pain and tenderness are common the headache can be less localized and tenderness less apparent.

I can count on one hand the number of patients who presented to my office with headache and subsequently found to harbor a brain tumor. All three had another cause for headache. This leads me to the issue of imaging studies.

### What are the clinical indications for use of imaging to evaluate headaches?

Although there should be no better situation than the use of imaging studies in headache to make a significant impact on the cost of healthcare, there remains a paucity of Class I evidence that would allow a definitive answer to this question.

Headache is one of the most common complaints of patients seeking medical attention; approximately 20% of women suffer from migraine alone. The vast majority of patients, even seen in a headache referral center such as mine, will suffer from primary headache disorders (migraine, tension-type and cluster headache). Of the remainder who are diagnosed with a secondary headache, analgesic rebound headache, now referred to as medication overuse headache, accounts for greater than 90% in our practice. The odds of finding a significant abnormality responsible for their headaches on imaging studies are exceedingly low. In patients fulfilling the criteria for migraine for example, the prevalence of significant intracranial abnormalities on imaging studies in meta-analysis was approximately 0.2%.[4] This would be consistent with my experience.

The Quality Standards Subcommittee of the American Academy of Neurology has published a practice parameter regarding neuroimaging in the evaluation of headache patients with normal neurological examinations.[5] The data of all studies reviewed were classified as Class III. The subcommittee concluded that in adults with recurrent headache that have been defined as migraine—including those with visual aura—with no recent change in pattern, no history of seizures, and no focal neurological signs or symptoms, the routine use of neuroimaging is not warranted. Again, these studies were performed on patients with a definite diagnosis of migraine and, as mentioned, apply only to those patients.

Since expert opinion is considered Class III evidence, I have decided to give you mine. In any of the following situations, imaging studies are mandatory.

a. Severe, sudden onset headache
b. Headache described as the worst headache ever experienced
c. New onset headache at age 50 or older
d. New onset headache associated with a history of cancer, immunodeficiency or systemic symptoms (e.g., fever, weight loss)
e. New onset headache that does not fit the strict criteria for a primary headache. (Remember the International Headache Society Criteria to diagnose migraine require five separate episodes)
f. Chronic headache with any new neurological sign or symptom
g. Chronic headache with significant change in severity or frequency
h. Headache associated with exertion, sexual activity or valsalva
i. Headache associated with fever or meningeal symptoms. (Do not delay LP waiting for an imaging study in a patient with a non-focal exam.)
j. Headaches that awaken the patient
k. Headache associated with head trauma. No clinical criteria have been developed that will totally exclude a structural lesion.
l. Any patient with such concern about a structural lesion that treatment will be ineffective until such a lesion is ruled out.

**It is also extremely important to ask about the use of over the counter meds since patients routinely omit these when describing the medications used to treat their headache.**

## How is Medication Overuse Headache best treated?

**Medication Overuse Headache (MOH)**[6] is defined by the International Headache Society Classification of Headache as:

A. Headache present ≥15 days/month fulfilling criteria C and D

B. Regular overuse for ≥3 months of one or more drugs (see table below) that can be taken for acute and/or symptomatic treatment of headache

C. Headache has developed or markedly worsened during medication overuse

D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication

1. Simple Analgesics (Acetaminophen, Opioids, NSAID's)
2. Combination Analgesics (Excedrin®, Fiorinal®, Fioricet®)
3. Ergotamines
4. Triptans (Imitrex®, Maxalt®, Relpax®, etc)
5. Other Vasoconstrictors, i.e. pseudoephedrine

In practical terms, this is a chronic daily or almost daily headache that develops in patients treating each headache with acute/abortive medications. It is most commonly seen with underlying migraine. The above criteria are for simple analgesics; i.e. triptans, ergotamines, opioids, acetaminophen. Combination analgesics only require 10 days per month. Since MOH requires a response to treatment, only a diagnosis of probable MOH can be made initially. It is should be recognized that the criteria are for days per month and not pills per month. I can't tell you how often I hear "but doctor I only take one Fiorinal® a day."

It is also extremely important to ask about the use of over the counter meds since patients routinely omit these when describing the medications used to treat their headache. Decongestants such as pseudoephedrine are commonly used to treat migraine mistakenly assumed to be "sinus headaches" and results in MOH as well. Antihistamines do not cause MOH, however we do prohibit use of antihistamine-decongestant combination medications due to the vasocontrictive effects of the decongestant. Some patients develop MOH during the treatment of another disorder. Daily analgesics for back pain or other ailments will result in the development of MOH in susceptible patients.

The most important reason to identify MOH is its effect on response to preventative treatment. Patients rarely respond to preventatives while they are in rebound and any preventative medication prescribed while the patient suffers from MOH cannot be considered an adequate trial. We have seen countless patients at The Headache Center who have not responded to prior treatments with preventatives. Once MOH has been eliminated, we will rechallenge patients with the same prophylactic medications with success.

There are no double blind placebo controlled studies of MOH treatment. The simplest treatment is to have a patient stop all offending medications, however after treating thousands of patients with MOH this is not a practical solution. I can guarantee you the first question you will be asked after you make this suggestion is "Doctor, what will I do if I get a headache?"

Our protocol at The Headache Center is outlined below:

1.) The most important aspect of treatment involves education. Many patients have never heard of the term analgesic rebound headache or medication overuse headache.

One method I employ is to actually show them the International Headache Society Classification of Headache. The list of headaches, even using a small font, takes up approximately 10 letter size pages. I flip through the pages saying, "these are all the headaches, we take all of them into consideration when making a diagnosis and there are criteria to make a diagnosis of each one." I then explain why they fit the criteria and that there is little hope of improving their headaches until the MOH is eliminated.

Education with respect to their underlying headache disorder is also necessary. Almost half of all patients with migraine have never been given a diagnosis, and if they have, they do not realize that migraine or other primary headaches are real diseases.

I spend a great deal of time explaining that migraine is a real disease in the same way Parkinson's is a disease. Like Parkinson's, migraine is a disorder of neurotransmitters. Both are clinical diagnoses and are not associated with any abnormalities of blood or imaging studies. It can be extremely therapeutic for a patient to know that what they are experiencing has a pathophysiological basis.

Once they understand and accept the diagnosis both MOH and their underlying primary headache disorder, we then discuss expectations of treatment. It is extremely important to manage expectations. Utilizing a comprehensive approach, a reasonable expectation is that we can reduce their headaches by 50%. We always try for more but they must realize that even after treatment they will continue to experience headaches.

2.) Sometimes, we delay initiating treatment several weeks to months if the patient's current personal circumstances would limit the chance of success. Once the program starts however, all offending medications must be stopped immediately. The only exception would be a patient on chronic narcotics, in which case we work in conjunction with a formal detox center. Patients who have MOH due to combination analgesics containing butalbital may receive a short course of treatment with phenobarbital to prevent withdrawal.

3.) The mainstay of medical treatment is prednisone.[7] Our protocol uses 60 mg for 6 days, 50 mg for 5 days, 40 mg for 4 days, etc., until completed. We seldom see significant side effects; however, since anxiety, restlessness and insomnia can occur, each patient is usually given a small prescription of diazepam to take prn. Anti-emetics are also prescribed.

4.) All patients are told to call us if they experience any headache that requires treatment. Treatment for such headaches is individualized. For those patients who experience severe headaches refractory to outpatient therapy, our inpatient program is utilized.

5.) The remainder of the treatment involves non-pharmacological treatment. The other members of the team include Physical Therapists and Behavioral Therapists. I can't emphasize enough the essential role each therapist plays. Our success is primarily based on our ability to work as a team. These are very challenging patients and medication alone is hardly ever successful. Most patients have associated cervical strain and muscle spasm and suffer from poor posture. Psychological comorbidity is also well documented. The prevalence of anxiety and depression is significantly higher in migraine patients especially those with transformed (chronic) migraine or medication overuse headache. In a study published in Headache,[8] seventy-eight percent of patients with transformed migraine had psychiatric comorbidity, including major depression (57%), dysthymia (11%), panic disorder (30%), and generalized anxiety disorder (8%).

6.) We recommend Vitamin B2 and Magnesium.[9,10]

7.) A headache diary is required of all patients

8.) All patients are seen in follow-up 2 weeks after the treatment is started and at that time, a preventative is usually started.

9.) We do not prescribe abortives until the headache frequency is less than 3/week. In our practice, all patients have abortives limited to avoid development of MOH.

MOH is a challenging disorder to treat but can be very rewarding for you and life changing for the patient after successful treatment.

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The author and/or spouse/significant other has no financial interests to disclose.

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EDITED BY ANA TUYA FULTON, MD

# Exciting News in the Area of Prevention and Screening

*Ana Tuya Fulton, MD*

**Mrs. G, a 72-year-old woman with a history of hypertension,** presents to your office for her annual physical. She comes with several questions related to prevention and screening after doing some on-line reading and hearing about the recent controversy over mammography. She wants to know how much longer she should continue to have mammograms, colonoscopies and other such screening testing. She is a vibrant woman who works two days a week as a volunteer at a local school and travels every few months to Florida, where she has a second home. She golfs and plays tennis regularly and has had no major medical illnesses or hospitalizations.

Mrs. B, a 72-year-old woman with a history of stroke, moderate dementia, hypertension, high cholesterol, osteoporosis and arthritis comes with her husband for her annual physical. Her husband is her primary caregiver, and Mrs. B requires assistance with dressing, eating and ambulating. She has recently developed incontinence, and her husband lets you know he recently hired a part-time nursing assistant to help him at home because it is difficult to leave her alone for any prolonged period of time. She is mostly homebound, though she still enjoys going out to church and lunch with her children on Sundays.

These two very different women come in for an annual physical examination. Most of the care they receive will be similar; e.g., physical exam, flu shots, laboratory evaluation, and medication reconciliation. However, when the question of prevention and screening is raised, the conversations will diverge and become more complex despite the patients being of the same age. Screening recommendations can be followed in most patients in cookbook fashion; however, as a patient ages, and especially if functional losses accumulate, the decisions become more complex and require individualized discussions of risks and benefits, treatment preferences, quality of life and life expectancy.

The topic of prevention has come into sharper focus recently with two major developments. The first, the passing of the Patient Protection and Affordable Care Act (ACA) will eliminate cost-sharing for Medicare beneficiaries for preventive health services, presumably allowing older adults to more often take advantage of preventive testing by removing financial barriers.[1] Second, the U.S. Preventive Services Task Force (USPSTF) in 2005 convened a geriatrics subgroup of its Methods Workgroup to redefine their methodology to better address the preventive needs of the older adult.[2] The first review to apply this new approach has just been published on the topic of fall prevention.[3]

Prevention has been murky for older and frail adults. For years, there has been a smaller evidence base to guide decision making because older adults are often excluded from the randomized trials used to formulate screening guidelines.[2] Additionally, the decision to screen or not is complicated by co-morbid illnesses, functional status, patient preferences and life expectancy. The outcomes that studies use to inform guidelines do not always apply to the older adult, who may not be looking to extend life or to prevent disease, but to maximize function and quality of life.[2] In addition, the outcomes that we sometimes strive for in older adults, such as improved function and quality of life, are difficult to measure as discrete outcomes in reviews and trials. The overarching questions that guide decisions can be summarized: Will the screening test diagnose the disease? Can the older adult tolerate the treatments that will be required? Will the person live long enough to benefit from the treatments, or will time-to-benefit exceed life expectancy?

The ACA will improve access for older adults to preventive services, but it will also open the proverbial "can of worms" for some patients who can now more easily get preventive services but for reasons of co-morbidities, life expectancy and others, might not benefit from them. The new methodology the USPSTF is using will help better equip both patients and providers to make these difficult decisions. Updated guidelines will now be more applicable to the older adult population and will provide more guidance on outcomes, including the nontraditional outcomes that are more applicable to the older adult population.

Specifically, the new methodology aims to address aging-specific issues for diseases prevalent in older adults. The USPSTF will aim to update recommendations with evidence that includes adults 65 years or older.[2] The Task Force is also proposing to better accommodate the multi-factorial nature of geriatric syndromes and the interventions used to treat them.[2]

The USPSTF changes and proposals are exciting ones that will benefit older adults. The two women above will profit from greater clarity in the future. For now, the recommendations made to each should take into account baseline health, life expectancy and patient preferences. Sadly, Mrs. B's functional status portends a poor prognosis, and her likelihood of benefitting from screening measures is small. If she is diagnosed with colon or breast cancer, treatment would be unlikely to extend her life and would substantially impair her quality of life and current level of functioning. She is able to stay at home with help, and still able to enjoy some activities with her family. Much luckier, Mrs. G has a considerably longer life expectancy, and with her high functional status, can still be expected to benefit from preventive services.

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### Disclosure of Financial Interests

The author and/or spouse/significant other has no financial interests to disclose.


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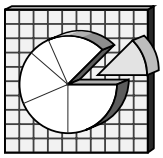
**9SOW-RI-GERIATRICS-032011**

The analyses upon which this publication is based were performed under Contract Number 500-02-RI02, funded by the Centers for Medicare & Medicaid Services, an agency of the U.S. Department of Health and Human Services. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government. The author assumes full responsibility for the accuracy and completeness of the ideas presented.

# Health By Numbers


Rhode Island Department of Health • David Gifford, MD, MPH, Director of Health

Edited by Samara Viner-Brown, MS


# Treatment for Asthma Symptoms and Prevalence of Persistent Asthma among Children Enrolled in Rhode Island's Managed Care Medicaid Program


*William McQuade, DSc, MPH, Deborah N. Pearlman, PhD, David S. Robinson, EdD, and Nancy Sutton, RD, MS*


**Asthma is a leading chronic illness among children in the United** States, and is disproportionately distributed in both prevalence and severity among low income and minority populations.[1,2,3,4,5] The National Committee on Quality Assurance (NCQA) has established a standardized definition for *persistent asthma* as one of the HEDIS (Health Plan Employer Data and Information Set) measures.[6] This measure is based on a patient's use of outpatient, Emergency Department (ED) and inpatient services, as well as the number of medication dispensing events over time.[7] The HEDIS measure for asthma is reported annually for both commercial and government-sponsored health plans,[8] and therefore this measure is well understood within the public health community. In addition, this measure can be easily calculated using most routine claims systems.

In this brief, we examine the prevalence of asthma symptoms treated in children aged 5-17 enrolled in Rhode Island's managed care Medicaid Program (RIte Care), as well as the prevalence of children who met HEDIS criteria for *persistent asthma.* We also describe the pharmacotherapy of NCQA identified medications used to treat asthma.

## Methods

Data for this brief are based on the Medicaid Managed Care Utilization Data Set (i.e., Encounter Data) from the RI Department of Human Services. Participating health plans are required to submit claims level data for all professional and institutional services as well as all outpatient prescriptions provided to Medicaid enrollees. The focus of this report is on services incurred during calendar year 2009 to children who were between 5 and 17 (inclusive) as of December 31, 2009.

The NCQA defines *persistent asthma* as any patient who is continuously enrolled for two years who met at least one of the following criteria during the measurement year and the year prior to the measurement year: 1) at least four outpatient visits with asthma listed as any of the diagnoses treated *and* at least two outpatient prescriptions for an asthma defined medication, 2) any ED visit with asthma listed as the primary diagnosis, 3) any inpatient admission with asthma listed as the primary diagnosis, or 4) four or more outpatient prescriptions for an asthma-related medication. Since the requirement for two years of continuous enrollment would exclude many RIte Care children with asthmatic conditions, we used a variation of the HEDIS measure

**Table 1. Medicaid Children Treated for Asthma and Meeting NCQA* Criteria for Persistent Asthma by Age and Gender. (Calendar Year 2009)**

| | Females (n=29,363) | | | | Male (n=30,873) | | | | Total (n=60,236) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5-11 (n=16,522) | | 12-17 (n=12,841) | | 5-11 (n=17,398) | | 12-17 (n=13,475) | | 5-11 (33,920) | | 12-17 (n=26,316) | |
| | # | % | # | % | # | % | # | % | # | % | # | % |
| **Patients Treated for Any Asthmatic Symptom** | 2,185 | 13.2% | 1,487 | 11.6% | 3,123 | 18.0% | 1,722 | 12.8% | 5,308 | 15.6% | 3,209 | 12.2% |
| **Patients Meeting NCQA Criteria for Persistent Asthma** | 1,021 | 6.2% | 574 | 4.5% | 1,540 | 8.9% | 737 | 5.5% | 2,561 | 7.6% | 1,311 | 5.0% |

*National Committee for Quality Assurance (NCQA) Health Plan Employer Data and Information Set (HEDIS) criteria

and focused on all children who met HEDIS criteria during calendar year 2009 who had been enrolled in RIte Care at any time during the measurement year.

Our second classification of an asthma case was defined more broadly. Children treated for any asthma symptom included: 1) any patient who received any asthma-related treatment (outpatient, ED or inpatient including procedures and radiology services such as pulmonary function tests or chest x-rays) with asthma listed as any of the diagnoses treated, 2) any patient who received any asthma-related medical supply or equipment (i.e., nebulizers), or 3) any patient with at least two outpatient prescriptions for an asthma-related medication.

A diagnosis of asthma was defined as an ICD-9 diagnosis code of 493.xx (i.e., a diagnosis of 493 with any fourth or fifth digit). Asthma medications were defined by a list of NDC codes provided by NCQA (www.ncaq.org, accessed on January 5, 2010). NCQA updated their medication list as of November 15, 2010.

## Results

Table 1 illustrates the distribution of asthma symptoms and persistent asthma by age (5-11 vs. 12-17) and by patient gender during calendar year 2009. Note that 15.6% of children 5-11 and 12.2% of children 12-17 were treated for any asthma symptom while 7.6% and 5.0%, respectively, met criteria for *persistent asthma*.

The prevalence of asthma varied by age and gender in both classification groups. The prevalence of asthma was higher among boys than girls and among children 5 to 11 years than for children between the ages of 12 to 17. Overall, about 45% of the children who were treated for any asthma symptom actually met HEDIS criteria for *persistent asthm*a.

Table 2 illustrates the distribution of the four NCQA criteria for persistent asthma among children aged 5 to17. Note that the vast majority (91.9%) of *persistent asthmatics* met criteria based on four or more dispensing events during the year, while 663 (17.1%) had four or more outpatient visits coupled with at least two dispensing events and 548 (14.2%) met criteria based on ED utilization. Furthermore, 94 children (2.4% of the *persistent asthmatics*) were admitted to the hospital with asthma as a primary diagnosis. Additional analyses showed that 72.5% of the children that met the HEDIS criteria of four or more outpatient prescriptions for an asthma-related medication (n = 2,580) did not meet any other criteria for persistent asthma (data not shown).

While rescue drugs such as the short-acting inhaled beta-2 agonists were the most common drugs used to treat any asthmatic, they were considerably more common among patients treated for asthma symptoms (67.8%) than for *persistent asthma* (43.3%) (see Figure 1). Controller drugs such as the leukotriene modifiers were more common among the patients treated for *persistent asthma* (26.2% vs. 5.25%), as were the inhaled corticosteroid combination products (6.7% vs. 2.5%). Other corticosteroid products were used about the same in both populations (23.5% vs. 24.4%). Other classes of drugs such as mast cell stabilizers, long-acting inhaled beta-2 agonists, antibody inhibitors, and methylxanthines were much less common (i.e., constituting less than 0.1% of all prescriptions filled). It is also important to note that about 88% of persistent asthmatics were treated with an NCQA preferred drugs (data not shown).

## Discussion

Our finding that 6.4% of RIte Care children met criteria for *persistent asthma* while as many as 14.1% have been treated for an asthma symptom is consistent with other studies that assessed asthma prevalence using Medicaid administrative claims data.[9,10,11,12,13,14] Also consistent with previous studies, we found that asthma was more common among boys than girls and among children 5-11 than children 12-17; confirming studies that suggest that asthma symptoms improve during adolescence and may not return in adulthood.[15] Children with more severe disease are more likely to have asthma as adults.

The vast majority of persistent asthmatics in our study met NCQA criteria based on their use of four or more prescribing events with only 17% receiving four or more outpatient visits coupled with two or more prescribing events. There were 548 who had an ED visit with asthma listed as the primary diagnosis and 94 had an inpatient admission with asthma listed as the primary diagnosis. We also found that asthma symptoms were more commonly treated with rescue drugs such as short-acting beta-2 agonists and that controller drugs were more common among persistent asthmatics. Approximately, 88% of patients with persistent asthma were treated with an NCQA preferred drug.

Our data suggest that while asthma continues to be a common condition treated among RIte Care children, many children are treated for incipient or transient symptoms that may not persist. Also, there is good evidence that most children with *persistent*

**Table 2. NCQA* Case Criteria for Persistent Asthma among Children 5-17 Enrolled in RIte Care, 2009 (n=3,872)**

| | # | % |
|---|---|---|
| Four or more outpatient visits and at least two asthma medication dispensing events | 663 | 17.1% |
| Any ED Visit with asthma as the primary diagnosis | 548 | 14.2% |
| Any inpatient admission with asthma as the primary diagnosis | 94 | 2.4% |
| Four or more asthma medication dispensing events | 3,559 | 91.9% |

*National Committee for Quality Assurance (NCQA) Health Plan Employer Data and Information Set (HEDIS) criteria

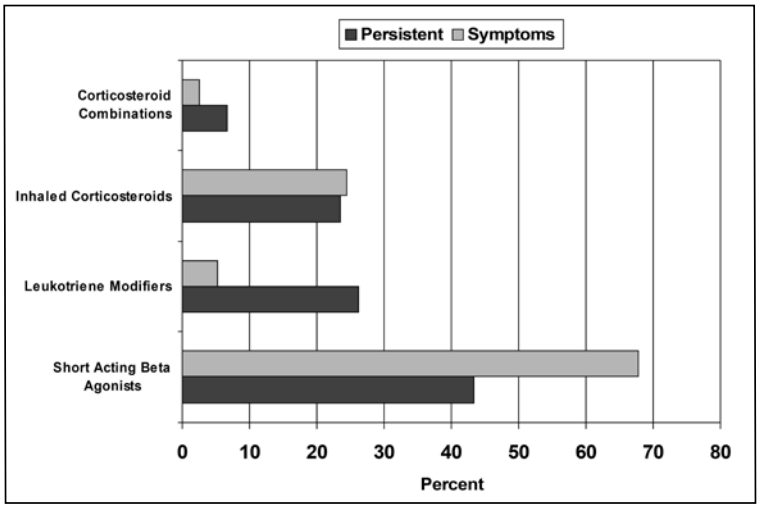



Figure 1. Distribution of Medications to Treat Asthmatic Symptoms and Persistent Asthma among Children Aged 5-17 Enrolled in RIte Care: Calendar Year 2009.

*asthma* are being pharmacologically managed without extensive outpatient visits. Future studies might focus on the role of routine preventive care in asthma maintenance. Finally, as asthma is a serious and potentially life threatening disease, continued oversight and monitoring are required to assure adequate care.


### Acknowledgements

This publication was supported, in part, by the Cooperative Agreement Award Number: 5U59EH000199-03 from The Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.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### Disclosure of Financial Interests

The authors and/or their spouses/significant others have no financial interests to disclose.


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# Images In Medicine

## Fever and an Expanding Pancreatic Fluid Collection

*Armando Bedoya, BA (MD '11), Matthew Hudson, MD, Julie H. Song, MD, and Edward Feller, MD, FACP, FACG*

**Pancreatic pseudocysts typically arise as complications of** acute pancreatic inflammation. When pseudocysts persist after recurrent attacks, cyst-related complications may occur with atypical, potentially misleading features. We report a patient with infection in a chronic, known asymptomatic pseudocyst. Clinicians should be aware of the diverse, possibly catastrophic sequelae of pancreatic fluid collections.

A 71-year-old male presented with 4 days of epigastric pain radiating to the back, anorexia, nausea and vomiting. Past medical history was significant for two recent admissions for unexplained pancreatitis that led to a pseudocyst formation (Figure 1). He had a history of hypertension, Parkinson's disease, and bipolar disorder. Medications included carbidopa/levidopa, lithium, and amlodipine. He denied alcohol use or history of liver disease. On admission, vital signs were normal; he was afebrile. Abdominal exam: mild epigastric tenderness to palpation. No stigmata of chronic liver disease, masses or portal hypertension. Serum lipase was normal. Abdominal ultrasound: no gallstones; magnetic resonance cholangiopancreatography (MRCP): no biliary or pancreatic duct abnormalities, no bile duct stones. Abdominal CT (Figure 2): peri-pancreatic inflammation with two pancreatic fluid collections, one that had increased in size from CT exam one-month prior and a second new, partially organized collection. He was stabilized on bowel rest and oral intake begun. On hospital day 5, he spiked a fever to 101$^{O}$ F. WBC count increased to 24,000. Repeat CT scan (Figure 3) showed two fluid collections markedly enlarged from the prior exam with a total transverse size of 18 cm. The fluid collections largely replaced pancreatic tissue and compressed his stomach anteriorly. Because cyst wall thickness was adequate, CT-guided percutaneous drains were placed with 1.5 L of purulent fluid collected. He was placed on Meropenem. *Klebsiella Pneumoniae* grew from cultures. Repeat CT (Figure 4) on hospital day 12 showed resolved fluid collections. Drains were removed. He was discharged to complete a 6-week antibiotic course.

### Discussion

In acute pancreatitis, increased ductal pressure causes duct dispruption with intrapancreatic enzyme activation. Leakage and excretion of pancreatic juice occurs into the pancreas, retroperitoneum, or peri-pancreatic space. Early in acute pancreatitis (< 4 wks), fluid collections are amorphous. Cyst walls are thin and drainage is hazardous because leakage of pancreatic juice would occur into the peritoneal cavity. A majority resolve spontaneously; however, in 5-15%, the collection can produce a profound inflammatory response along serosal surfaces of adjacent organs, resulting in a fibrous pseudocapsule with a defined wall. This process takes between 4 and 8 weeks, at which point this collection is termed a pseudocyst.

Pseudocysts may remain asymptomatic independent of size or duration. However, very large cysts, as in our patient, may be more likely to become symptomatic from expansion or complications, such as infection, rupture, bleeding, vascular

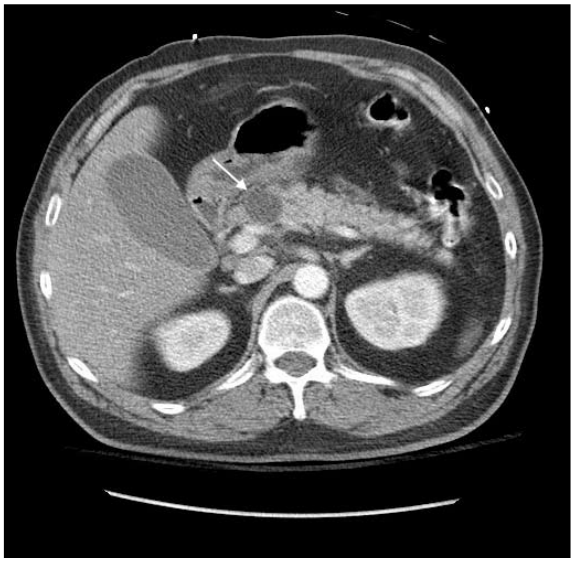

Figure 1. Axial contrast-enhanced CT image 1 month prior to admission. Homogenous 2 cm fluid collection (arrow) at the neck of pancreas.

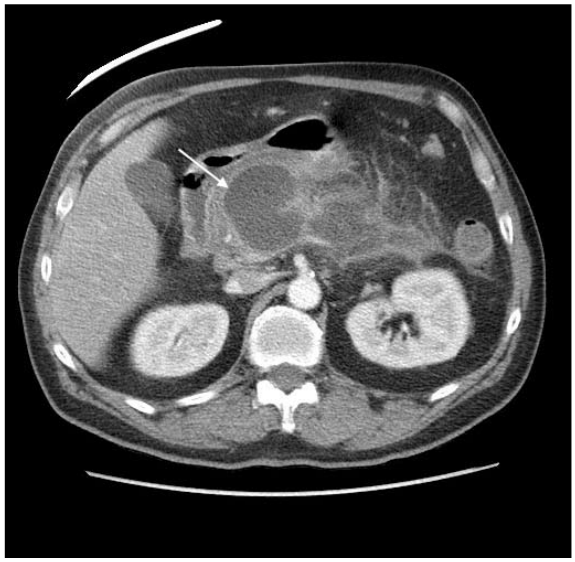

Figure 2. CT at admission. Peri-pancreatic inflammation with enlarged fluid collection at neck of pancreas with enhancing wall (arrow) and a new partially organized collection at the pancreatic body and tail.

Figure 3. CT on hospital day 5. Further enlargement of two fluid collections, replacing pancreatic tissue and compressing the stomach (arrow).

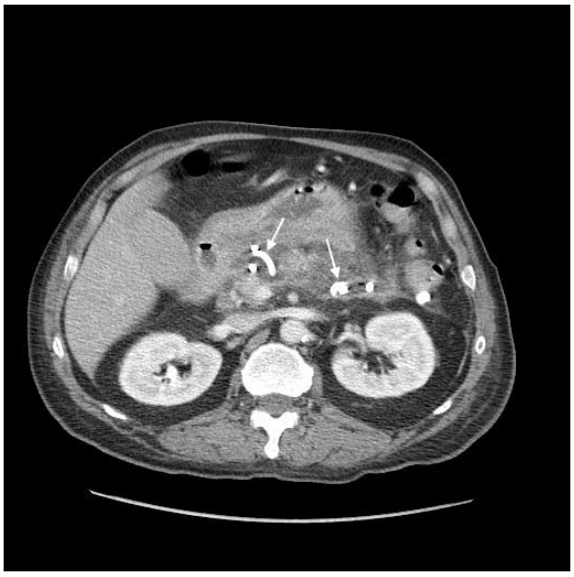

Figure 4. CT on hospital day 12. Resolution of fluid collections following percutaneous CT-guided drainage. Drains (arrow) were removed after CT.

thrombosis or obstruction of adjacent structures such as the bile duct, duodenum or colon.

Fever in patients with pancreatic fluid collections must be distinguished from biliary infection as well as from other pancreatic fluid collections: Pancreatic abscess where purulence predominates, infected pancreatic necrosis where necrosis predominates, or a cystic pancreatic neoplasm.

Occurrence of fever at day 5 due to pancreatic infection is atypical. Infection in pancreatic fluid collections is a secondary phenomenon, typically requiring at least 7-10 days to develop from a sterile collection . However, his pseudocyst was chronic; potential infection was possible at any time.

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### Disclosure

The authors and/or their spouses/significant others have no financial interests to disclose.


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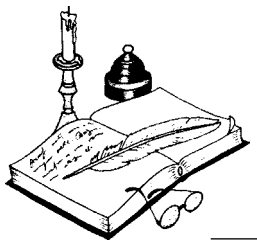

# Physician's Lexicon

## An Intersection of Languages

**Contemporary medicine and its current** vocabulary is the grateful recipient of the lexical riches of two successive, classical languages: Greek and Latin. Inevitably, then, roots derived from these Classical tongues may look much like each other but carry differing meanings. These resulting ambiguities are best illustrated by the *ped-*, *pedi-*, and *pes-* roots, from the Latin, generally meaning foot. And the *podo* – from the Greek, also meaning foot; but then there is, from the Greek, *pais-* or *paido-* (in English, spelled as *pedo-* or *paedo-*) meaning boy or child of either gender.

The Latin root, *ped-*, generates such English terms as pedal, peduncle, pedometer, pedestal, pedestrian, pedicure and pediment, each pertaining to the foot, or uses of the foot. The word, pedigree, is derived from the French phrase *pie de grue*, meaning a crane's foot because it resembles the genealogic marks used in defining family trees. Orthopedics is literally straight, or corrected, feet, as is orthodontia, meaning straightened teeth.

But then we encounter the words, pediculosis (louse-ridden) and pediculocide (an agent used to kill lice.) The parasitic genus, *Pediculus*, is composed of many-footed insects and hence its name.

The Greek, *podo-* root also gives rise to numerous words pertaining to the foot: words such as podagra (an obsolete term for gout), podiatry, podium and podophyllum (literally, a plant with leafed feet.)

The *paedo-* or *pais-* Greek root pertaining to male child in general, yields English words such as pediatrics (the *iatrikos* root meaning physician or healer), pedagogue (a teacher, with the Greek root, *agogos*, meaning to lead, to guide and sometimes to flow forth as in words such as cholagogue), pedant (a teacher of children), pedantic (an adjective describing the trait of excessive scholarliness; Ambrose Bierce once described pedantry as dust shaken out of a book and into an empty skull) and pederasty (sexual molestation of children).

The *pes-* root, pertaining to the foot, is used in such medical phrases as pes abductus (talipes valgus) and pes cavus.

Pessimism, the belief that the evil in this world outweighs the good, comes from the Latin, *pessimus*, meaning worst and probably stems, earlier, from the Latin *ped's mal*, meaning a bad foot or a bad foundation. The English word, pejorative, is a descendant of *pessimus*.

Peddle and peddler, on the other hand, come from a Germanic root meaning basket.

– Stanley M. Aronson, MD

Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

# Vital Statistics

Edited by Colleen Fontana, State Registrar

## Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

| Underlying Cause of Death | Reporting Period | | | |
|---|---|---|---|---|
| | March 2010 | 12 Months Ending with March 2010 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 197 | 2,352 | 223.3 | 3,107.0 |
| Malignant Neoplasms | 192 | 2,244 | 213.1 | 6,405.0 |
| Cerebrovascular Diseases | 40 | 450 | 42.7 | 867.5 |
| Injuries (Accidents/Suicide/Homicde) | 48 | 605 | 57.4 | 10,497.5 |
| COPD | 47 | 489 | 46.4 | 490.0 |

| Vital Events | Reporting Period | | |
|---|---|---|---|
| | September 2010 | 12 Months Ending with September 2010 | |
| | Number | Number | Rates |
| Live Births | 1,030 | 11,985 | 11.2* |
| Deaths | 768 | 9,127 | 8.5* |
| *Infant Deaths* | (2) | (80) | 6.7# |
| *Neonatal Deaths* | (2) | (65) | 5.4# |
| Marriages | 778 | 5,969 | 5.6* |
| Divorces | 333 | 3,213 | 3.0* |
| Induced Terminations | 322 | 4,251 | 354.7# |
| Spontaneous Fetal Deaths | 30 | 609 | 50.8# |
| *Under 20 weeks gestation* | (22) | (544) | 59.6# |
| *20+ weeks gestation* | (8) | (65) | 5.4# |

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,053,209.

(c) Years of Potential Life Lost (YPLL).

***Note:*** *Totals represent vital events that occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

THE RHODE ISLAND MEDICAL JOURNAL
The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publications Committee
VOLUME 1
NUMBER 1
PROVIDENCE, R.I., JANUARY, 1917
PER YEAR $2.00
SINGLE COPY, 25 CENTS

## Ninety Years Ago, March 1921

Frank Bailey Smith, MD, upon his retiring as president of the Kent County Medical Society speaks on the subject of fads in medicine—popular diagnoses and treatments. Among his list he includes: "it was found necessary to put nearly every woman's uterus into a glass jar, which was the proper place for it; but when they found it shortened life, it was only recommended for those who desired no more children or actually had malignant disease." He also takes note of "fad" diagnoses of scrofula, peritonitis, ossification of the arteries, and distention of the transverse colon—among others. He then focuses on the more recent "yeast fad" that has grown out of an interest in vitamins. He quotes Dr. Hershberg of New York: "Happily there is always at hand a simple, cheap, plain, every-day-and-Sunday-go-to-meeting food, viz., the yeast cake, which contains a liberal supply of vitamins A fresh yeast cake is certainly an ideal food, if eaten freely, flavored or not, three times a day, before or with meals. In its composition are to be found mineral fertilizers for human use, vitamins, water soluble 'B' for sugars, starches and egg-white like stuff." Drolly, Dr. Smith suggests that, at long last, a near-universal panacea has been uncovered.

In an editorial, the writer laments members of the medical profession who show a certain disdain for erudition. Acknowledging exceptions to the argument, the writer continues: "Do we wish to relinquish our claim to being one of the learned professions? It is true that we cannot all be literary men of the first order, nor can we all discuss literature and the classics with the most erudite of our patients; but we can all, we trust, by a little earnest effort, learn to express ourselves with an approximation of what 'unity, coherence and force' upon which our teachers of rhetoric were wont to insist."

After conveying the warmth of a home-made photograph sitting on a desk, another editorial discusses the *Journal of the American Medical Association* and the *Rhode Island Medical Journal*: "So with the two journals, the *Journal of the American Medical Association* is the formal and foremost journal of the day and you can not possibly afford to be without it, but your state journal is also important. It should be of even more interest to you for it should give you news of your own brother practitioners whose problems and joys are much the same as your own. There should be in it a certain friendly intimacy that you would not expect in a national publication. In other words it should correspond to the home-made picture."

In a short, light feature entitled "Ether and Lavender: Dissertation on Brains" it is observed that "One of the most singular things about brains is that everyone is sure that he is the possessor of the best," and "The difference between brains of the human variety and that of the lower animals is that one, by process of educational training has the power of continuity of thought and consecutive thinking; but this must, at times, be proven."

## Fifty Years Ago, March 1961

In a letter to the editors, Dr. A Lloyd Lagerquist writes in response to an editorial in the February issue regarding generic vs trade name drugs. Conducting an experiment on generic prescriptions and cost to patients, he prescribed the generic medication to thirty patients, then surveyed the actual medication they received. In twenty-seven cases, the pharmacist supplied, and charged for, the trade name version while three provided the generic pill but did not charge the patient any less. Dr. Lagerquist does not draw any conclusions beyond his own personal observations, but notes that there is "much more to this problem."

An editorial notes that forty-thousand patients across America wear medic-alert bracelets. The non-profit Medic-Alert Foundation maintains a numerical card file containing medical information and data on members and is available on a twenty-four hour basis by collect phone call. The editorial closes with: "This then is the dog-tag which worked so well in the Services, prettied up for the ladies and adapted to civilian use. It is a great improvement over the cards so many diabetics have carried and often lost in the past. The Medic-Alert Foundation, for its manifest public service, merits the support of physicians everywhere.

In "Through the Microscope," it is noted that "more than 5,000 college and university students taking part in the 1960-61 National Intercollegiate Debate program, are currently discussing the proposition: "That the United States should adopt a program of compulsory health insurance for all citizens." The Health Insurance Institute developed and disbursed an "insurance reference kit" for use by debaters, speech department, and school libraries.

## Twenty-Five Years Ago, March 1985

Continuing to address alcoholism in Rhode Island, Thomas Romeo, director of the then-named Rhode Island Department of Mental Health, Retardation and Hospitals, notes that with an estimated 54,000 to 68,000 persons in Rhode Island who are "Alcohol troubled" that the view of alcoholism has shifted from a perception of moral weakness to "a complicated disease process which affects all strata of society." In "Family-oriented treatment of alcoholism" by Michael Liepman, MD, Ted Nirenberg, PhD, and William T. White, RN, MSN it is further noted from the start that "The comprehensive multidimensional treatment of alcoholism has become an accepted concept only witin the recent past. One of the latest innovations in alcoholism treatment has been the emergence of intensive family therapy."

A special report from The Committee on Impaired Physicians of the Rhode Island Medical Society focuses on those illnesses that tend to be treated inadequately when occurring in physicians such as alcohol and drug dependency, depression, severe anxiety, and other behavioral disturbances. They point out that other "organic illnesses" such as heart disease often receive optimal treatment and do not represent a problem in neglect.

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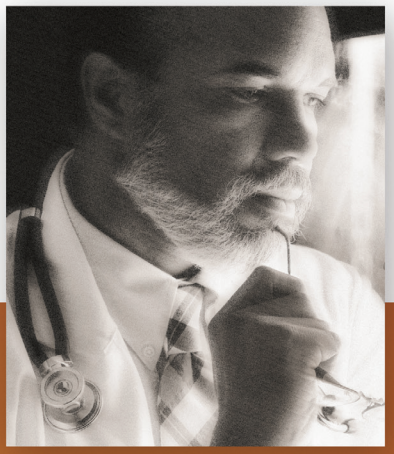

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