Athens Kidney Center
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RETURN SERVICE REQUESTED

SUBCLINICAL HYPOTHYROIDISM

About 5% of the population has subclinical hypothyroidism (most commonly from autoimmune thyroiditis), and its diagnosis is relatively easy: the relationship between circulating free T4 levels and TSH is log-linear, therefore a 2-fold change in T4 levels will cause a 100-fold alteration in TSH profile. High TSH levels infer hypothyroidism, thyroid hormone resistance syndromes, ineffective TSH activity (in central hypothyroidism phenotypes), TSH assay interference (from heterophile antibodies) or recovery from non-thyroid clinical illness. It is unclear if there are any benefits in treating subclinical hypothyroidism (with serum TSH usually between 5-10 mIU/L) though there is some indirect evidence that pregnancy in subclinical hypothyroidism is associated with fetal morbidity. Overall, therapy may be indicated in the following situations:

1. Higher risk of progression to clinical hypothyroidism (i.e. over 4% yearly), as may be suggested by family history, clinical symptoms, previous history of overt hypothyroidism and positive thyro-peroxidase antibodies.
2. Past or present history of fetal wastage or fetal morbidity.
3. Specific phases of life, notably early childhood and pregnancy.
4. Presence of palpable goiter.
5. Presence of thyroid-related medical comorbidity: coronary artery disease with "combined" hyperlipidemia; clinical depression or refractory bipolar disease; infertility/anovulatory status or dysfunctional uterine bleeding.

CHOOSING A VASOPRESSOR IN THE ICU

1. Refractory Heart Failure/Cardiogenic Shock: (a) Milrinone/*Primacor* at 50 mcg/kg IV over 10-12 mins then 0.375-0.75 mcg/kg/min acts to increase myocardial contractility via phosphodiesterase-3 inhibition but also relaxes vascular smooth muscle leading to profound hypotension; (b) Dobutamine/*Dobutrex* at 0.5-1.0 mcg/kg/min IV slowly titrating upwards to 20 mcg/kg/min (maximum) acts like milrinone mainly via beta-1 agonist stimulation (increased heart rate & contractility) and subsidiary beta-2 agonist effect (causing moderate hypotension)
2. Septic/Other Shock Syndromes: (a) Norepinephrine/*Levophed* at 2-30 mcg/min IV acts as alpha-1 adrenergic agonist (and subsidiary beta-1 adrenergic agonist effect) to primarily increase systemic vascular resistance (and secondarily improve cardiac contractility); (b) Dopamine acts at different receptors at different doses, primarily as dopamine agonist at <5 mcg/kg/min (natriuresis), beta-1 agonist at 5-10 mcg/kg/min (enhances myocardial contractility and heart rate), alpha-1 adrenergic agonist >10 mcg/kg/min (systemic vasoconstriction).
3. Other Hypotensive States: (a) For neurogenic shock/loss of vascular tone/post-anesthesia hypotension, consider Phenylephrine/*Neosynephrine* at 40-180 mcg/min which only acts peripherally (no cardiac effects) to increase vascular tone via alpha-1 adrenergic stimulation; (b) For cardiac arrest/anaphylaxis, consider Epinephrine at 1-10 mcg/min IV or 1 mg (dispensed as 10 mL of 1:10,000 solution) q 3-5 mins PRN which acts primarily as beta-1 agonist (with milder beta-2 and alpha-1 effects) to stimulate the heart (no peripheral effects at low doses).
4. Vasopressin/Anti-Diuretic Hormone: used most often in combination with vasodilatory inotropes for dose-dependent vasoconstriction (peripheral effects only) at 40 IU IV as single dose or 0.01-0,04 IU/min IV (being an intense vasoconstrictor, it should not ordinarily be used in concert with Phenylephrine, and caution is advised with Norepinephrine)

the
SECOND OPINION

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FROM THE EDITOR

Doomsday predictions notwithstanding, the world was never going to end in 2011, and the chances of Armageddon come 2012 are looking equally tenuous. Which is, of course, a reminder that failed human predictions are as commonplace - and embarrassing- as snake-charming evangelicals along the Appalachian trail. Witness the claim in 1899 by Charley Duell, commissioner of Patents, that everything that could be possibly invented had already been done. Or the ballsy assertion by renowned Yale economist and connoisseur, Irving Fischer, in 1929 that the stock market had attained a permanently high plateau. Or the equally preposterous claim from the Wall Street Journal in 1996 that Bill Clinton, enmeshed in controversy and congressional combat, was guaranteed to lose to any Republican candidate that didn't drool onstage: citizen Dole didn't drool, candidate Clinton didn't lose.

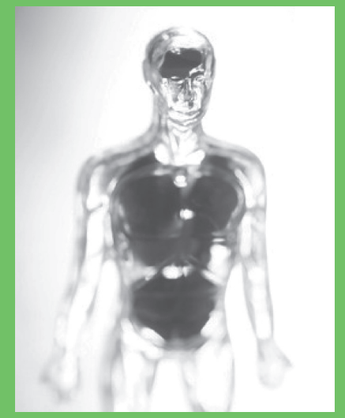
But 2011 was awash with an all-pervading aura of surrealism: crowds overflowing into Arab streets, giving voice to long-bottled frustrations, spewed forth like aged wine as violence spread across the Maghreb. The once-mighty economies of the Eurozone, serially disemboweled in public reenactments of *sepuku*, now beholden like so many banana republics to the IMF and good graces of Angela Merkel. Subjected to a fate worse than death, the United States endured a public rebuke by Standard & Poor in an orchestrated downgrade of her credit rating. A dazed public watched the televised spectacle of Muammar Gaddhafi's mutilated body, finally free of hubris and pathos, in its final stages of *rigor mortis*. A new nation-state was born amidst the anomie of Southern Sudan, with little fanfare or histrionics, but then again, unlike the ill-fated Republic of Biafra, there was no oil as a bone of discontent.

It was a very strange year. The "99 percenters" who presumably stood to gain the most from Obamacare liberalism, turned out to be the most vehemently opposed to "social engineering" laced with perceived government overreach. The chattering classes were in turn, entranced and titillated by scandal in high places: the curious case of Dominique Strauss-Kahn, erstwhile chief of the IMF, in dalliance with a lowly hotel maid; Citizen Cain, the man who would be President, tripped up by so many discarded bikinis from a half-forgotten past; the bathroom shenanigans of Jerry Sandusky, gridiron great and alleged pederast, was all it took to topple Joe Paterno, iconic football legend and sovereign of Penn State, from his pedestal far above the laws of god and men. And there was Donald Trump, celebrity billionaire and original Birther-in-Chief, offering his considerable skills to a lukewarm nation as presidential nominee, before changing his mind, prior to leading the charge in authenticating President Obama's birth certificate, before fronting an ill-fated soon-to-be-televised Presidential debate-that-never-was, before finally removing himself from public view amidst recriminations, tantrums and affronted sensibilities. The cognoscenti insist The Donald might still throw in his hat- or wig, depending on whom you asked- into the ring as an Independent candidate. Dr. Conrad Murray, cardiologist and house-doctor to Michael Jackson, got 4 years for his pains in ministering unto the sleepless. The tenth anniversary of 9/11 came and went, *sans* color-coded terror alerts and *sans* you-know-whom: somewhere in a cement-laden paradise under the northern Arabian sea, someone must be feeling pretty shortchanged. Frothing Occupy Wall Street crowds, the dreaded "99 percent" of our citizenry, surged into the treacherous night, braving both elements and unregistered felons to reclaim America; it's never been clear who took America hostage in the first place. One of my favorite denizens, Borders Bookstores, declared bankruptcy. The global population breached 7 billion: take that! Reverend Malthus. Fukushima's nuclear reactor imploded. The infamous scandalsheet, News Of The World, harlequin frontispiece of an ailing Murdoch empire, was found entrapped in its own chicanery.

The world lost Christopher Hitchens, plummy-voiced English raconteur and wit, a devout skeptic and flame-thrower of the left; Andy Rooney, choleric muse of Sunday nights, finally succumbing to old age, of all things; Dr. Steve Fennell, father, doctor, intellectual, friend. He was an Athens dentist. Everybody loved him. I will miss him.

It has been quite a year. Merry Xmas to you and yours. I should see you again, Friday lunch-time, at the CME lounge.

Beze Adogu, MD, Ph.D, FACP



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CYCLIC VOMITING SYNDROME

Recurrent vomiting is not an uncommon condition, but is poorly recognized and inappropriately treated in most cases. A timely review by Helazi & McCallum, *Aliment Pharmacol Ther*, 2011, reviews the current state of knowledge about this perplexing condition. First, recurrent vomiting can be due to a multitude of causes, and each has to be considered and ruled out with a competent history, physical examination, lab investigations (including the time-honored pregnancy test, lipase/amylase, liver function tests, abdominal imaging, gastric motility tests, etc). Second, the differential considerations include: migraine (including "abdominal migraine" with pain), cannabis-associated hyperemesis syndrome, endocrinopathy (Addison's disease, thyrotoxicosis), subacute gastrointestinal disorders (peptic ulcer disease, hepatitis, biliary stenosis, pancreatitis especially with pseudocyst formation, inflammatory bowel disease, gastric dysmotility disorders, recurrent subacute appendicitis, duodenal atresia/diverticulum/web, intermittent intussusception), chronic narcotic abuse, hyperemesis gravidarum/premenstrual syndrome and ovarian cysts, gallbladder dyskinesia, neurologic disorders (including migraine, increased intracranial pressure, familial dysautonomia, subdural effusions/hematoma, slit/anomalous ventricle drainage) and psychiatric morbidity (from bulimia/anorexia, major depression, conversion disorders, factitious illness or Munchausen's). Third, the diagnosis of cyclic vomiting syndrome (CVS) is a diagnosis of exclusion; patients present with functional, stereotypical attacks of unrelenting vomiting at any age (though onset is more commonly in childhood), often associated with migraine (without aura), showing a slight female predominance, and is construed as a reflection of brain-gut maladaptation, possibly through abnormal neuro-endocrine pathways in those genetically predisposed by virtue of inheritable mitochondrial DNA mutations. CVS is often triggered by infections (of the upper respiratory tract or sinuses), physical/emotional stress, medications (such as narcotics and cannabinoids), sleep deprivation, motion sickness, diet (containing chocolate, MSG or other condiments) or menstrual periods (the so-called katamenial vomiting of adulthood). Clinical disease is quadri-phasic: an inter-episodic asymptomatic period of relative normalcy; a prodromal period (of nausea, lethargy, ptyalism, anorexia, pallor); a brief period of intense and repetitive vomiting (typically more than 3x each hour, each episode lasting less than 7 days, and each attack occurring more than 3x each year) which may be associated with an acute stress response (hyperglycemia, hyper-adrenergic status, mild hyperthermia, tachycardia, diaphoresis, diarrhea and mild leucocytosis) as well as predictable complications (of Mallory-Weiss tear, peptic esophagitis, gastric prolapse). Fourth, treatment is tailored towards the disease phase: avoidance of putative triggers is the mainstay of management during the inter-episodic phase; prophylaxis with cyproheptadine, propranolol, tricyclic antidepressants, and possibly, other anti-migraine drugs; Zofran/Phenergan, hypnotic-sedatives (to induce sleep, and hopefully, abort the cycle), chlorpromazine/Phenergan as abortive therapy; other considerations include early NSAIDs use (based on theory of prostaglandin excess), coenzyme Q plus Elavil (as suggested by Boles et al, *BMC Neurol*, 2010, based on mitochondrial energy theory), and of course, early IV rehydration and correction of emesis-induced electrolyte deficits.

CHOOSING RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKERS

RAAS blockers are not equivalent: ARBs block angiotensin II at the receptor level, which presumably results in more complete effector antagonism; ACE inhibitors are able to block angiotensin II generation via ACE enzyme pathways but not chymase-mediated and other non-ACE pathways. Also, ACE inhibitors block kininase, therefore augmenting the effects of the vasodilator substance, bradykinin. Current AHA guidelines suggest that ACE inhibitors should be used in preference to ARBs in treating heart failure with reduced ejection fraction (Lindenfeld et al, *J Cardiac Fail*, 2010) though several randomized trials show no difference in clinical outcomes between either drug group (Jong et al, *J Am Coll Cardiol*, 2002). The effect of RAAS antagonists in heart failure with preserved ejection fraction is unclear, with several studies such as the CHARM -Preserved Trial suggesting a null or limited/minimal effect (Yusuf et al, *Lancet*, 2003). Others have suggested that not all ARBs are equal: Candesartan is superior to Losartan in outcomes (Eklind-Cervenka et al, *JAMA*, 2011). A recent study by Zhang et al, *Am J Cardiol*, 2011, shows that in older patients in heart failure with preserved systolic function, use of ARBs was associated with lower mortality and fewer hospitalizations compared to ACE inhibitors. Maybe, it's time to reassess RAAS antagonists for superiority.

TIME TO STOP INTENSIVE BLOOD GLUCOSE CONTROL

A new study by Boussageon et al, *BMJ*, 2011 adds to previous analyses from Gerstein et al, *N Engl J Med*, 2008 and Ray et al, *Lancet*, 2009, on the clinical futility of intensive blood glucose control in type 2 diabetes mellitus. Compiling data on 18,315 patients randomized to intensive glycemic control and 16,218 patients on "standard glycemic therapy, Boussageon et al found no significant effect of intensive therapy on either all-cause mortality or cardiovascular death, despite the high cost of severe hypoglycemia (relative risk 2.33 in intensive treatment group). Interestingly, there was a minor increase in the incidence of congestive heart failure in the intensive treatment group, which raises the question: does hypoglycemia itself contribute to myocardial asthenia, were sulfonylureas complicit in cardiac myofibril dysfunction via its effect on ATP-sensitive K channels, or was this a side-effect of specific hypoglycemic drugs (such as thiazolidinediones)? If intensive glycemic therapy has no macrovascular or microvascular benefits, why do we persist in subjecting our diabetic patients to this practice?

INTERNAL MEDICINE RESIDENCY IS A BITCH

A study by West et al, JAMA, 2011 reiterates what we instinctively (and experientially) knew: residency training is a bitch. A total of 16,394 participants were surveyed on quality of life issues. Not surprisingly, poor quality of life scores, emotional exhaustion and educational debt were linked to poor in-service exam scores. About 15% of participants described life as "as bad as it can be", about 51% had at least 1 symptom of "burnout", newer trainees tended towards more emotional exhaustion, and a third of participants were unhappy with their overall life-work balance. The study suggested that international medical graduates were less likely to experience burnout: those, I presume, were the doughty comrades who realized it was a privilege to learn and practice medicine in the United States (warts and all)!

IT'S THE ECONOMY, MY FRIENDS

It turns out that low household income as well as a sudden reduction in household income is strongly associated with mental disease and suicidality, according to Sareen et al, *Arch Gen Psych*, 2011. In a prospective, longitudinal study involving 34,653 participants over 3 years, investigators found that after adjusting for confounding factors, the majority of Axis I and II mental diseases was associated with low income, particularly mood disorders. A drop in household income was was linked to mood disorders also as well as anxiety disorders and substance use.

DRUG ADHERENCE DEPENDS ON DRUG CLASS

A meta-analysis by Kronish et al, *Circulation*, 2011, studies the impact of anti-hypertensive drug class on compliance and medication adherence. As all internists know, diagnosing hypertension is 1 thing, maintaining patients on adequate treatment is something else. Using medication refill data from local pharmacies, the summation of studies indicate that adherence was poor after 1 year of drug treatment; prescription drug adherence was worst with beta-blockers and diuretics; ACE inhibitors and ARBs were the most faithfully used. I do think our patients are trying to tell us something...

PREDICTING PROGRESSION OF CKD TO ESRD

CKD is common, but most patients never attain ESRD. Indeed, more patients die from cardiac causes following diagnosis of CKD than ever embark upon renal replacement therapy (by dialysis). In an era of limited resources, we ought to focus our energies on CKD patients who are more likely to progress to ESRD. Tangri et al, *JAMA*, 2011 provide a starting point. Using a cohort of 8,391 CKD patients, they were able to develop a predictive formula based on age, gender, eGFR (degree of renal failure), albuminuria, serum albumin, serum bicarbonate (estimate of metabolic acidosis), serum calcium (estimate of failure of vitamin D activation), serum phosphate (estimate of renal osteodystrophy).

SHOULD WE REVASCULARIZE OR SIMPLY MEDICATE?

The debate over revascularization (CABG or PCI) in coronary artery disease rages: added to the fray is the role of revascularization in CAD with left ventricular systolic failure. The STICH trial reported by Velazquez et al, *N Engl J Med*, 2011, finally provides good (but preliminary) answers. A total of 1,212 CAD patients with ejection fractions <35% were randomly assigned to medical treatment only or medical treatment plus CABG. Over the study period of 5 years, 41% of the medical therapy group died (cardiac causes of death were implicated in 33% of subjects) as did 36% of the medical therapy plus CABG group (cardiac causes in 28% of subjects). Conclusion: there was no difference in all-cause mortality based on addition of CABG to standard medical therapy in CAD with systolic L ventricular failure. Surgery is not superior to medications alone.

HIV SANS HIV: THINK HIV-2

Recent reports highlight the diagnostic puzzle presented by HIV-2 infection where serologic testing is limited to HIV-1 only or commercial HIV RNA viral load assays fail to detect HIV-2 RNA copies (Almaghrabi et al, *Ann Saud Med*, 2011). HIV-2 is endemic in West Africa, has a lower infectious potential than HIV-1 (therefore spreads more slowly within the population, despite similar routes of viral transmission), has a slower rate of clinical progression to AIDS, has a weaker response to some anti-HIV drugs (especially protease inhibitors and non-nucleoside reverse transcriptase inhibitors, which building pocket for HIV-2 is different enough to confer innate resistance to the drug) and may have a more muted lymphocyte response (in comparison to HIV-1) to HAART.

IF ONLY YOU WOULD TAKE THESE DRUGS...

More news from the medications adherence department: Lo Re et al, *Ann Intern Med*, 2011, report that patients suffering from hepatitis C virus infection who were more adherent to pegylated interferon and ribavirin were more likely to achieve both early virologic response (> 2 log10 decrease in HCV RNA at 12 weeks) and sustained virologic response (undetectable HCV RNA at 24 weeks post-completion of drug therapy). Sadly, drug adherence slowly declined over time, but concurrent treatment with growth factors or thyroid supplements appeared to boost overall drug adherence.

NEVER TAKE DNR ORDERS LIGHTLY

Kazaure et al, *Arch Surg*, 2011, compared 4,128 surgical patients with DNR orders and 4,128 age/procedure-matched controls without: DNR patients were predominantly white, elderly and female, and also had 36% longer hospitalizations, 5% higher complication rates and 14.5% higher mortality rates. DNR status was found to be an independent predictor of mortality, as were frailty, advanced age and pre-operative sepsis. Surgeons should be aware of these uniformly poor outcomes in DNR patients before wielding the knife.

LESSON FROM THE ED: ASEPTIC MENINGITIS PICTURE IN AIDS PATIENT WITH ESRD

Aseptic meningitis is an uncommon clinical syndrome, but warrants aggressive evaluation when uncovered. The possibilities- and likelihood- is somewhat wider with immuno-compromise as well as delayed drug excretion, as exemplified by this case. It is important to remember that most cases of aseptic meningitis will spontaneously resolve without specific treatment. The diagnostic considerations are:

1. Partially-treated bacterial meningitis (history of recent/prior antibiotic therapy) and para-meningeal bacterial infections.
2. Viral meningitis (including enterovirus, LCM, mumps, HIV-associated meningitis, HIV-associated vasculitis, herpes simplex virus type 2 [type 1 commonly causes encephalitis, type 2 causes meningitis], et cetera)
3. Granulomatous meningitis: tuberculous meningitis; sarcoidosis; ?medications (NSAIDs, IV immunoglobulins, anticonvulsants, antibiotics [especially beta-lactam and Septra], OKT3/monoclonal antibodies)
4. Neurosyphilis/latent syphilis; Lyme disease (history of tick bite or demonstration of erythema chronicum migrans); Ehrlichiosis (history of tick bite); Rocky Mountain Spotted Fever (history of tick bite).
5. Cryptococcal meningitis; brucellosis; leptospirosis; coccidioidal meningitis;
6. Non-infectious meningitis: recurrent meningitis of Mollaret (lymphocytic meningitis characterized by plasma cells found on Paps stain of CSF, etiology often HSV or idiopathic); vasculitis; meningeal carcinomatosis (from lymphomas, acute leukemias and few solid tumors); Behcet's disease; Vogt-Koyanagi syndrome; Whipple's disease