

# the SECOND OPINION

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## FROM THE EDITOR

One year ago, we embarked upon a journey to modernize- or as some would say, overhaul- health care in these United States. The legal instruments have since been signed into law at Washington, with a little bit of fanfare and a generous outpouring of bad blood. Lost in the partisan wrangling was the near-universal sense of optimism that heralded the new Obama administration in 2008. It was in many ways, the Washington remake of the myth of Ganymede: those whom the gods love, as with New Year resolutions, are destined to die young. In the temple of our politics, the past never dies, the future never comes, and bickering comes as naturally as respiration.

Still, it is unsettling that despite the palaver and threats of repeal, no one seems to fully know- or understand- the provisions of the health care bill. In democracies, as in "open" marriages, wherever there is a deficit of facts, rumor and conspiracies naturally fill the vacuum.

Reasonable men can agree that the present health care system provides too little health for too much money, in comparison to other Western democracies. Where we may differ is in the prescribed treatment of choice. I suspect it will take a sustained, non-partisan approach to address those issues, which will, most regrettably, probably be deferred until the blood lust of the 2012 presidential campaign is assuaged. Any solution ought to involve improved efficiencies of care delivery; a realistic economic stake by patients (on whose behalf large amounts of money are daily disbursed); universal access through a universal single-payor insurance (the myth of altruistic insurance companies, such as the myth of "no insurance" -an excuse for serial emergency care abuse- are merely distractions); comprehensive tort reform (which should lead to the death of "defensive" medicine); restricted emergency care (EDs should not become detox centers or prescription refill clinics by default); less invasive procedures and more hands-on clinical care (in contrast to our culture of high-tech diagnostic "fishing" expeditions); universal generic drug use; health care rationing (which should be based on the twin concepts of futile care and meaningful recovery); and reduced provider payments (which is, not unexpectedly, anathema to physicians and hospitals alike). But first, the name calling, bomb throwing and other varieties of legislative mischief must stop. Invoking the mythic specter of "death panels" does not advance the argument.

Truly, the present times call for bold, innovative measures. This is no time to "hedge" the bets or play to a shiftless "Independent voter" gallery. With 1 and a half wars currently being waged overseas, and at least 2 more (Iran and North Korea) looming over the horizon, this is no time for obfuscation or half-measures or maudlin compromise. As Aneurin Bevan once remarked in another context, "those who walk down the middle of the road, are most likely to get run over". The past, as embodied by Medicare (and supplemented by Medicaid), has served us very well; but that was then. This is the time to recreate a new future for the coming age. Whether it wears the darker hues of President Obama, or the variegated shades of Speaker Boehner is completely beside the point. Keeping the status quo in health care delivery is no longer a viable option for this republic. Except, of course, you subscribe to the miserable conclusion of Jean-Paul Satre, in "Being and Nothingness", that all human actions are equivalent; and all are on principle doomed to failure. In that case, I'll see you Friday lunch-time, at the CME lounge. And a Merry Christmas to you and yours.

*Beze Adogu, MD, Ph.D, FACP*

## ONCE A CAESAR, ALWAYS A CAESAR?

The reasons for the perplexing variability in rates of Caesarean sections, even within the same country (and presumably, similar medical traditions) and even within domains of "socialized medicine" (such as the UK's National Health Service) remain obscure. In the UK, there is a North-South divide (Caesarean birth being more common in the South) and it appears that most of the variability is linked to emergency caesarean section. A paper by Fiona Bragg et al, British Medical J, 2010, documents that 23.8% of singleton births were by caesarean section; 71% had undergone previous caesarean section; 90% had a breech presentation; and differences in local obstetric practice was more pronounced for emergent rather than "elective" caesarean surgeries. Now, if only we could extrapolate those findings to the United States....

## LOW HEART RATE AS THERAPEUTIC TARGET

The SHIFT trial reports that baseline heart rate correlates with worse composite end-points, including death and hospitalizations (Michael Bohm et al, Lancet, 2010). Indeed, risk measurably increased by 3% for each 1 beat/min elevation in resting heart rate. Lowering the heart rate under 60/min with Ivbravadin resulted in better outcomes, presumably by improving cardiac contractility, optimizing energy supply whilst reducing energy expenditure, and long-term, reducing the risk of atherogenesis, all of which are dependent on ambient heart rate.

## TRANSFUSE OR NOT?

The data on blood transfusion gets more conflicting by the minute.

- Item: healthy young adults can tolerate isovolemic anemia down to a hemoglobin of 5 g/dL (RB Weiskopf et al, JAMA 1998).
- Item: tolerance threshold is raised by obstructive coronary arteriosclerosis, but exact level is unclear, though experimental models suggest that this lies somewhere with hemoglobin under 10 g/dL (H Yoshikawa et al, Am J Cardiol 1973) which is supported by finding of increased mortality amongst Jehovah's Witnesses with CAD where hemoglobin is under 10 g/dL (JL Carson et al, Lancet 1996).
- Item: routine blood transfusion to maintain an imaginary threshold of hemoglobin >8 g/dL is associated with a higher mortality in ICU setting (SV Rao et al, JAMA 2004).
- Item: There should be no restriction to blood transfusions in face of an acute myocardial (ischemic) event (PC Hebert et al, Crit Care Med 2001).
- Item: all anemia are not equal- outcomes depend not only on severity of anemia but also on underlying medical diseases, especially tissue perfusion, organ dysfunction and cardiovascular disease. Item: all blood is not equal- aged RBCs (usually from prolonged storage) are associated with high levels of cytokine release, decreased deformability, decreased 2,3-diphosphoglycerate levels, impaired oxygen transport/delivery and higher intravascular hemolytic rates.

## LEAVING THE HOSPITAL AMA

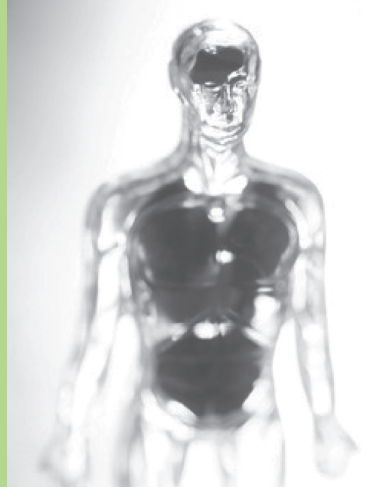
Every patient has the right to refuse medical care and unilaterally terminate any clinical intervention being proposed on his behalf, except in very specific instances (such as mental incompetence, specific harm to self or others, etc) defined by law and statute. Leaving AMA accounts for 2% of all hospital discharges. Those at high risk for leaving AMA are disproportionately Black, usually young, male, lacking in insurance coverage, no identifiable primary/family physician, living in poverty, and with a history of previous AMA discharges and/or substance abuse. Leaving AMA results in several predictable results: high frequency of re-admission typically within 15 days of discharge, and usually with the same diagnosis/complaints; high risk of later morbidity or death; high levels of staff/physician frustration; inefficient use of hospital/institutional resources, and high overall costs. Appropriate management involves a recognition of the deep-seated psychological factors that trigger this behavioral pattern (depression? anxiety? fear? loss of control? feelings of dependence?); addressing substance abuse problems; identification of motivation factors or specific triggers that lead to self-discharge; obtaining informed consent for all planned interventions; preparation for a safe discharge; arrangements for follow-up management with resolution of any transportation and/or commitment issues.

## ONE SMALL STEP AGAINST HIV

The role of anti-retroviral drug chemoprophylaxis was better defined in a recent publication (RM Grant et al, N Engl J Medicine, 2010) where 2499 HIV-negative men (transgender women as well as men-who-have-sex-with-men) were followed over a period of 2.8 years (median = 1.2 years). After education on HIV acquisition, condom use, et cetera, they were randomly assigned to either a combination therapy with emtricitabine (FTC) plus tenofovir (TDF) or placebo. Even at the time of enrollment, 10 participants were already HIV-positive, and during follow-up 100 more became HIV-positive, 36 in the FTC-TDF drug group and 64 in the placebo. At the cost of drug-induced nausea amongst the FTC-TDF study participants, chemoprophylaxis represented a 44% reduction in HIV acquisition over the prescribed interval. The shockingly high infection rates (10 HIV-positives during randomization!) suggest that this is clearly a start, but certainly not the solution.

## THE END OF COUMADIN CLINICS

In another blow against continued Coumadin use, a "non-inferiority trial" in acute DVT, to be published this week by the EINSTEIN investigators (N Engl J Medicine, 2010), compared a simple, fixed-dose regimen of oral Rivaroxaban (a potent factor Xa inhibitor) to "conventional therapy" with subcutaneous enoxaparin followed with oral Coumadin. This open-label, randomized trial enlisted 3449 participants, and significant clinical complications were experienced by 2.1% of the Rivaroxaban group in the short-term, dropping to 1.3% after prolonged follow-up, whilst 3% of the "conventional therapy" group experienced clinical events acutely, rising to 7.1% in the long-term. Major bleeding occurred only in 0.7% of Rivaroxaban users. I guess we won't see too many new Coumadin clinics sprouting up any time soon.



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## WHEN DIURETICS FAIL

*Diuretic treatment is the cornerstone of volume management in heart failure, the leading cause of hospitalizations amongst the elderly. A substantial proportion of heart failure patients are resistant to diuretic drugs, which also connotes a poor long-term prognosis. Common reasons for diuretic resistance are:*

- *Therapeutic misadventure: failure to establish a true dry weight or surrogate target (such as 1-pillow orthopnea, trace ankle edema, absence of rest dyspnea), failure to slowly titrate diuretic dose to “ceiling” levels, failure to eliminate adverse drug-drug interactions (notably NSAIDs or “salt pills”);*
- *Mucosal edema: edema of GI tract can substantially reduce the absorption of p.o. diuretics in heart failure patients, who may not necessarily have ascites or anasarca; IV drug administration is a useful bridge in such cases;*
- *Failure to adopt a low-salt diet (which should be less than 2 gram sodium daily);*
- *Therapeutic non-compliance: whilst a pill-count or verification of drug refills at the pharmacy are commonly used, the absence of hypokalemia, “contraction” metabolic alkalemia or hyperuricemia are useful indicators of non-compliance;*
- *Kidney failure: reduced renal function reduces drug delivery to the kidneys, and accumulation of uremic/organic anions as well as exogenous acids such as NSAIDs, sulfonamides, beta-lactam antibiotics, methotrexate and anti-virals which may individually compete with loop diuretics for transport via the organic anion transporter (OAT) at the proximal tubules;*
- *Hypoalbuminemia: albumin acts as “carrier” for loop diuretic delivery to organic anion transporter, hypoalbuminemia impedes drug delivery to the kidneys;*
- *“Braking phenomenon”: initial fluid mobilization is followed acutely (within days/weeks) by hyperfunction of Henle’s loop resulting in the re-establishment of a new steady state and reduced diuresis, which can be overcome by increasing drug dose or switching to another drug class; it is crucial to distinguish this from tachyphylaxis, which follows chronic persistent drug therapy, resulting in renal adaptation (via hyperplasia of specific tubular segments with increased numbers of ion pumps/co-transporters) and antagonism of diuretic effects;*
- *Secondary hyperaldosteronism: release of aldosterone in response to acquired volume/salt deficit from diuresis, resulting in distal tubular sodium retention; this effect should be distinguished from hyperfunction of vasopressin/ADH receptors within the distal tubules, as well as post-diuretic enhancement of sodium retention caused by activation of angiotensin II and/or alpha-1 adrenoceptors at the proximal tubules immediately following termination of diuretic effect (this can be overcome by using long-acting diuretics or increasing the frequency of drug administration).*

## BIOMARKERS IN MEDICINE: RULES OF ENGAGEMENT

A good clinical biomarker must satisfy the following criteria: (1) Fast, easy to use, adaptable, easy to understand/interpret; (2) Universally available; (3) Serum/blood levels are temporally related to pathologic event (peaks at presentation, clears after acute event); (4) High sensitivity (able to identify all cases of pathology); (5) High specificity (able to exclude all cases that are not pathologic); (6) Generally affordable; (7) Levels correlate with severity of disease or clinical prognosis.

- However, no known biomarker fits all 7 requirements. A paper by Chan & Ng, BMC Medicine, 2010, reviews the current state-of-the-art for biomarkers in acute MI:
- Any chest pain patient with troponin T <0.01 and Co-peptin <14 pg/mL does not have MI (negative predictive value = 99.7%)
  - High levels of B-type natriuretic peptide (and mid-regional pro-Atrial natriuretic peptide as well as serum adrenomedullin) indicate high myocardial stress patterns, and are predictive of later heart failure/mortality following acute MI
  - Growth differentiation factor-15 (GDF-15) is predictive of poor outcomes in acute MI; those patients should be quickly stratified to early invasive management

## DEBATING COENZYME Q10

Ubiquinone, a.k.a. coenzyme Q10, is an anti-oxidant as well as part of the mitochondrial electron transport chain, a critical component of oxidative phosphorylation. Coenzyme Q10 is derived partly from dietary intake, and also from endogenous biosynthesis through the mevalonic acid pathway (which is blocked by statins); coenzyme Q10 deficiency is associated with skeletal myopathy. A recently published paper from the CORONA data-base by John McMurray et al, J Am Coll Cardiol 2010, confirms that low serum levels of coenzyme Q10 is common in severe heart failure especially amongst the elderly, but such low levels do not independently predict outcomes in heart failure, and further reduction in coenzyme Q10 levels by statin treatment does not worsen cardiac outcomes. The take-home is that low coenzyme Q10 levels might be an effect rather than cause of heart dysfunction.

## UNDERSTANDING NEPHROTOXICITY

Studies published by Yaremi Quiros et al, Kidney International, 2010, show that sub-nephrotoxic doses of a nephrotoxic substance (gentamycin) sensitize test animals to future renal failure when later challenged with another sub-nephrotoxic drug. Such pre-sensitization could be clinically identified through high urinary levels of ganglioside M2 activator protein. The importance of this finding is the chemical identification of a potentially vast sub-group of “at risk” patients for acute kidney injury (0.6-2.3% of “no risk” patients develop renal insufficiency following contrast challenge); the potential to prevent clinical disease in that vulnerable population by careful drug audit; and a timely reminder to avoid nephrotoxic “dualism” (e.g. adding NSAIDs to an aminoglycoside antibiotic) even if those are given days/weeks apart.

## WIN SOME, LOSE SOME, OTHERS NEVER CHANGE

Despite widespread publicity by CMS on the sins of unacceptable surgical complications, otherwise known as “never events”, data from Philip Stahel et al, Arch Surg, 2010 show those “never events” are still with us, and perversely enough, are actually becoming more common. Those “never events” are surgery on the wrong patient; surgery at the wrong site; and, performance of the wrong procedure. Prevention of “never events” focuses on 3 elements: (1) pre-procedural verification; (2) clear marking and isolation of the surgical site; and (3) a “time out” interval to reassess and review each case before the procedure starts. Fishing in a treasure trove of self-reported physician insurance data in Denver, CO, Stahel et al found that the root causes of “never events” depend on the specific complication that occurs. For wrong-patient surgeries, errors in diagnosis were found in 54% of cases, errors of communication in 100%, and errors involving diagnosis by internists in 24%. For wrong-site surgeries, errors in judgment were noted in 85% of cases, failure to observe “time out” in 72% of cases, and surgery by orthopedic surgeons in 22.4%.

## POST-SURGICAL COGNITIVE DYSFUNCTION

Stable cognitive decline following surgery is not uncommon in the elderly, though the exact mechanisms are clouded. Anesthesia, cerebral micro-emboli and peri-procedural micro-infarcts have been suggested, though direct proof of causation is lacking. Those cognitive changes must be differentiated from the labile cognitive dysfunction of acute delirium. A study by Yanjie Wan et al, Crit Care Med, 2010, shows that cerebral dysfunction following surgery in mice is related to surges in pro-inflammatory cytokines, serum increases in amyloid precursor proteins (which act as acute phase reactants), astrogliosis in the brain, beta-amyloid deposition in the hippocampus and tau-protein phosphorylation. Those features can be blocked by anti-inflammatory drugs.

## STRESS ULCER PROPHYLAXIS: WHAT COMES NEXT?

Stress ulcers are multiple, superficial gastric ulcers commonly found in ICU patients. Stress ulcer prophylaxis has evolved as standard of ICU care in the United States, though there is little data as to its efficacy in preventing gastric bleeding in comparison to placebo. Acid suppression of the upper GI is associated with a higher risk of hospital-acquired pneumonia, higher rates of C. difficile colonization, and a higher propensity to drug-drug interactions. A systematic review of the literature by Paul Marik et al, Crit Care Med, 2010, suggests that as development of stress ulceration has become less common, the proper management should be early introduction of enteral feeds (within 48 hours of admission) and use of H2-blockers (rather than PPIs) for prophylaxis; however, the unexplained finding of higher mortality in studies where both enteral feeding and H2-blocker treatment were used concurrently should give all cause for concern.

## SPLURGING ON VITAMIN D

Vitamin D is a fat-soluble pro-hormone which regulates calcium-bone metabolism as well as 200+ genes, affecting myocytes, pancreatic cells, neurones, immune cells, liver and endocrine cells; its biological effects follow serial hydroxylation at the liver and kidneys respectively. Most foods do not contain vitamin D, though industrial fortification is routine in the United States, and natural ergocalciferol (vitamin D2) is found in milk, egg yolk, fish and mushrooms. Some vitamin D can be synthesized in the skin, following exposure to ultraviolet B light. Vitamin D acts as an anti-oxidant and anti-inflammatory effector.

At least 50% of the older population have low serum levels of vitamin D, a finding associated with multiple diseases of uncertain linkage: diabetes mellitus (both type I and type II disease), multiple sclerosis, coronary artery disease, lung infections, dementia, falls, osteoporosis, kidney failure, congestive heart failure, et cetera. Vitamin D supplementation appears to reduce fracture risk, being measurable from 400 IU daily, going up to a maximum effect noticeable at doses of 800 IU daily (Bischoff-Ferrari et al, Arch Intern Med, 2010). Those who receive mega-doses are paradoxically at higher fall/fracture risk (KM Sanders et al, JAMA, 2010) but cases of overt toxicity are unproven, though such high doses are associated with a high risk of hypercalcemia and nephrolithiases (Vieth et al, J Steroid Biochem Mol Biol 2004).

## CHECKING OUT LOW SERUM TSH

A low serum TSH can only be interpreted in the context of free T3/free T4 levels; 1 without the other is a recipe for conflict. There are 5 typical scenarios:

- Low TSH plus low T3/T4: central hypothyroidism from pituitary disease vs. very severe “sick euthyroid syndrome” (in ICU setting);
- Low TSH plus high T3: suggests true T3 thyrotoxicosis, which may be endogenous (therefore, high serum thyroglobulin levels) or exogenous (with low serum thyroglobulin levels);
- Low TSH plus high T4: a radio-iodine uptake test is crucial to diagnose thyroiditis/ectopic thyroid tissue or exogenous thyroid intake (low radio-iodine uptake) vs. autoimmune Graves’ disease/toxic nodular goiter (high radio-iodine uptake);
- Low TSH plus low T3: “euthyroid sick syndrome” (free T3 is lowest, TSH is borderline depressed, free T4 is normal) vs. TSH-suppressing medications (effects are usually transient, and will not result in persistent hypothyroidism, except if there is another underlying cause, such as “sick euthyroid syndrome” in ICU patients; drugs include amiodarone, steroids, octreotide, dobutamine/dopamine);
- Low TSH plus normal T3/T4: could represent mild (subclinical) disease resulting in higher levels of either T3 or T4 if tests are repeated in 6-12 weeks vs. normal physiologic variant (outside the “normal” Gaussian distribution curve for TSH) vs. “euthyroid sick syndrome” (free T3 is most significantly depressed, TSH only marginally low, and free T4 tends to be normal)

## PROPER DIAGNOSIS OF MALARIA

S. Taylor et al, JAMA, 2010 provide an timely review on the clinical pitfalls of malaria diagnosis. In summary, 3 billion people live in malaria-endemic zones and 250 million develop clinical malaria each year, killing approximately 1 million of those. About 1300 cases are reported each year in the United States, primarily amongst “returnees” from malarious zones. Diagnosis in the US depends on blood smears, rapid antigen tests or PCR molecular bioassays; yet, over 50% of cases are initially misdiagnosed because the diagnosis of malaria was never considered (KC Kain et al, Clin Infect Dis 1998). Conversely, in most developing countries, diagnosis is often clinical, and data suggests that it could be wrong in 90% of cases (M Amexo et al, Lancet, 2004). The prevalence of malaria (as defined by parasitemia) in febrile patients resident in malaria-endemic countries range from 6-66% depending on age (higher in children), locality (higher in sub-Saharan Africa) and constellation of symptoms/findings (higher if splenomegaly/hepatomegaly). Similar figures were noted in febrile “returnees” from malarious countries. Clinical indices were notorious for mistaken diagnosis: absence of respiratory/GI symptoms (aiming to exclude pneumonia or gastroenteritis) did not help improve accuracy of malaria diagnosis; presence of classic features (e.g. chills, rigors, headaches, myalgias) did not improve the diagnostic yield for malaria. The only useful findings that may suggest malaria are pallor (in children), hepato-splenomegaly, thrombocytopenia and jaundice. The validity of a point-score system based on simple symptomatology developed at Gambia was found inconsistent in prospective studies (KA Bojang et al, Trop Med Intern Health 2000; D Chandramohan et al, Trop Med Intern Health, 2001). Overall, febrile patients in malarious zones tend to be over-diagnosed with malaria, and “returnees” to non-malarious zones tend to be under-diagnosed.

## AED USE IN HOSPITALS

Automated external defibrillators (AEDs) are potentially life-saving in out-of-hospital cardiac events but are less useful within the hospital setting, in large part because the vast majority (80%) of in-house cardiac events are “non-shockable” rhythms which do not respond to defibrillation, such as cardiac asystole and pulseless electrical activity (MA Peberdy et al, Resuscitation 2003). A study by PS Chan et al, JAMA 2010 shows that patients receiving defibrillation with AED were more likely to die than those not subjected to AED intervention, irrespective of the basic underlying rhythm. The reasons for those poor outcomes are less certain, but might include interruption of CPR or manual chest compressions, ineffective or delayed deployment of AED device by untrained personnel in the hospital setting, defective or otherwise disabled AED devices, and a trend towards a passive “by-stander” attitude by hospital staff during AED hook-up. This new study must be balanced against another (albeit smaller) study showing improved in-hospital survival rates with AEDs (AM Zafari et al, J Am Coll Cardiol 2004).

## NOT TO BE MISSED: PSEUDO-HYPOALDOSTERONISM

Syndrome of different pathologies/diseases where the kidney appears to be unresponsive to aldosterone, superficially mimicking hypoaldosteronism. Classic symptoms of hypoadrenalism are present with paradoxically high levels of plasma renin activity as well as plasma aldosterone (except in Gordon’s syndrome, where both aldosterone and PRA levels are low). Pseudo-hypoaldosteronism is thought to be rare, and is probably misdiagnosed as doctors often do not consider this possibility in the routine evaluation of hyperkalemia.

Diagnostic ingredients: childhood onset (except in Gordon’s syndrome which presents in adulthood), low or normal BP (except in Gordon’s syndrome where hypertension is typical), positive family history (may be sporadic, autosomal dominant or autosomal recessive), presence of hyperkalemia, hyperchloremic metabolic acidosis and normal kidney filtration (normal GFR).

Type I disease results from a mutation either in the epithelial sodium channel (autosomal recessive sub-type) or mineralocorticoid receptor (autosomal dominant sub-type), with clinical presentation in early infancy with renal salt wastage resulting in dehydration, vomiting, salt-craving, hyponatremia, inappropriate natriuresis/polyuria (high urinary Na in face of hyponatremia).

Type II (Gordon’s syndrome is the adult phenotype) is due to a mutation affecting the so-called WNK (With No Lysine Kinase) proteins, which are physiologically inactivated by aldosterone; WNK proteins regulate both the expression and activity of several carriers, namely the Na-Cl co-transporters, renal outer medullary K (ROMK) channels, epithelial sodium channels and chloride co-transporters. Gordon’s syndrome is peculiar because of its adult onset, presence of arterial hypertension, low PRA and aldosterone levels, evidence of plasma volume expansion thought due to activation of the thiazide-sensitive Na-Cl co-transporter at the distal nephron: the kidneys therefore behave as a “chloride shunt”, and treatment is with life-long thiazide administration.

Pseudo-hypoaldosteronism may also be acquired from disorders that lead to ablation of the renin-aldosterone-angiotensin axis, impaired aldosterone synthesis or (distal) tubular resistance to its effect from medications (e.g. NSAIDs, heparin, cyclosporin, beta-blockers), urinary tract obstruction/infection, interstitial/lupus nephritis, sickle cell nephropathy and amyloidosis.

## WEIGHTY MATTERS

The relationship between weight (as assessed by BMI, a mathematical construct of weight in kgs/height in meters squared) and all-cause mortality is a J-shaped curve (doesn’t that sound familiar?). Using a Cox regression analysis, Berrington de Gonzalez et al, N Engl J Medicine, 2010, analyzed mortality in 1.46 million adult Caucasians, discovering that the ideal BMI for extended survival was 20-24.9. So, now you know.