Athens Kidney Center
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RETURN SERVICE REQUESTED

TREATING "NORMOTENSIVES" AS HYPERTENSIVE

Recall a lively debate over the merits of treating pre-hypertension in Athens at the time of our first publication last year? Here comes a timely meta-analysis by Thompson et al, *JAMA*, 2011, showing that in normotensives/pre-hypertensives with underlying cardiovascular disease, anti-hypertensive therapy reduced the risk of heart failure (which was the most significantly decreased), as well as strokes, acute myocardial infarction, cardiovascular events and all-cause mortality (least impressive change, yet improved by ~15%). Are we ready to sign on for anti-hypertensive use for those pre-hypertensives at highest risk?

TRYING TO SEPARATE EPILEPSY FROM PSEUDO-SEIZURES

Sooner or later, we all get to witness a pseudo-seizure. Pseudo-seizures are quoted to account for about 1/5 of all "first seizures" and 1/3 of all "refractory seizures" requiring hospitalization. More confusingly, 10% of patients with pseudo-seizures also have "true" epilepsy. Dissociative (pseudo) seizures, as is common with all dissociative (conversion) disorders, suggest a strong feeling of disconnection from both the patient's environment (derealization) and body (depersonalization). Triggers may be physical or psychological, but many cases lack any obvious triggers. Whilst a video-EEG provides fairly irrefutable proof of diagnosis, other tests are only suggestive, not diagnostic. Even a "normal" surface EEG during a seizure does not rule out "true" epilepsy, and reliance on elevated serum prolactin during "true" seizures is neither universal nor specific, sometimes "spiking" during pseudo-seizures too. Psychologic impairment may be a primary manifestation of temporal lobe epilepsy, and parasomnias/abnormal sleep behavior may occur in REMS sleep. Findings that suggest a pseudo-seizure: slow onset with fluctuating course; tightly shut eyes/mouth; side-to-side or thrashing motions or other dramatic body movements; gradual onset of episode; extended duration of episode (true seizures typically last only for seconds or a couple of minutes); recall of episode after attack; absence of injuries (true seizures are associated with tongue bites or shoulder dislocation, but pseudo-seizures are associated with skin abrasions from rubbing on the floor); tachypnea (true seizures are more often associated with apnea); absence of incontinence.

TREATING CLINICAL DEPRESSION

Major (unipolar) depressive disorder is a common, heterogenous clinical disorder, with variable presentations (elderly patients tend to somatize, specific presentations are culture-dependent), variable clinical course, variable response to treatment, and a poorly established pathogenesis. Its prevalence is 6-8% of the adult population, with an estimated lifetime risk of 20% in women and 12% in men. Current hypothesis favors decreased serotoninergic transmission within the CNS, specifically at the dorsal raphe nucleus, left prefrontal cortex and limbic system. The diagnosis of major depression is purely clinical, but general diagnostic acumen is abysmally low: physicians often fail to inquire about depressive symptoms; patients are more comfortable discussing "somatic" complaints; Mitchell et al, Lancet, 2009, showed in a meta-analysis that when primary care physicians attempt to diagnose major depression, its positive predictive value is only 42%, and negative predictive value is 86% (translation: for 100 patients, 10 patients with depression will be diagnosed, 10 patients with depression will not be detected, 15 patients without depression will be wrongly diagnosed as depressed). All anti-depressants work, each drug will be effective in ~30% of cases; the key to proper management rests on (1) proper diagnosis; (2) consideration of other non-drug interventions (watchful expectancy especially in new-onset cases, counseling, psychotherapy, light therapy especially in seasonal affective disorder, acupuncture especially in pregnancy, electro-convulsive treatment if immediate improvement is mandatory, transcranial magnetic stimulation, vagal nerve stimulation); (3) appreciation of lag-time between drug initiation and clinical effect (clinical response takes at least 2-6 weeks); (4) proper drug risk-benefit analyses (risks of SSRIs outweigh benefits in children, with exception of Prozac; all antidepressants except Wellbutrin and Lexapro are associated with weight gain, the most adipogenic being Remeron and Paxil; Lexapro is typically the most potent anti-depressant in the SSRI class; Wellbutrin and Serzone have the least deleterious effect on libido; SNRIs are associated with increased BP readings; atypical anti-depressants may be associated with seizures [Wellbutrin], somnolence [Desyrel], weight gain [Remeron], gastro-intestinal adversity and sedation; tricyclic antidepressants are toxic at high doses and associated with anti-cholinergic side effects; MAOIs risk hypertensive emergencies with tyramine); (4) low threshold for psychiatric referral (especially in atypical presentations or if patient is either suicidal or unresponsive to therapy).

the
SECOND OPINION

March 2011 | *A monthly medical newsletter for the Athens medical community* | Volume 2, #3

FROM THE EDITOR

A wise old man once told me that disease, any disease, was the social expression of pathology. I suppose he meant that clinically overt manifestations of disease were refracted through the prism of geography, co-morbidity, culture, expectations, nutrition, behavior and social resources. Therefore, disease and illness are not synonymous. Our response to common afflictions suggest the absence of "a common final pathway" to health outcomes. Consider: measles and other common viral exanthema of childhood are but mere nuisances in much of the West, but typically trigger a spiral of secondary infections, malnutrition and death in developing countries. As you would recall, the manifestations of AIDS amongst gay males on the West Coast were so different from findings observed amongst IV drug abusers on the East Coast that several investigators wrongly concluded that they were dealing with different diseases. Which explains, in a round-about sort of way, why Carl Duesberg still has pie on his face.

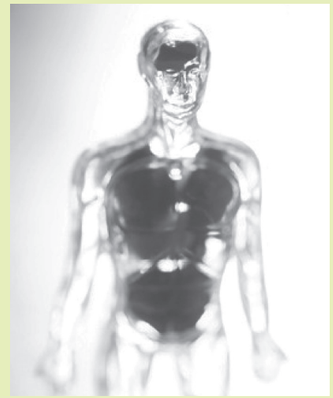
To understand disease, one must become familiar with its pathology. However, to treat disease, one should understand its social connections. One of the unintended consequences of the British 1870 Education Act, providing free and compulsory primary education to British subjects, was the clinical recognition of "brain fag", an unlikely name for an even more unlikely syndrome of "brain fatigue" amongst over-achieving teens. With time, aided by a less hysterical contemplation of Virgil and similarly obscure Latin texts, those clusters of culture-bound recidivism vanished. A generation later, similar social constructs led once more to the recognition of "brain fag" amongst Australian immigrants, in the colonies of the New World, gaining its full clinical expression one hundred and twenty years on in colonial West Africa, where a ready facility with the demands of Western culture and education was literally, the difference between life and death. As in England, brain fag has since quietly disappeared from the African neurological landscape. The same could be said for similar cultural expressions of disease such as amok (common in typically reticent Asian populations), vanishing testes syndrome (in cultures where manhood, or lack thereof, is measured in inches), kwashiokor (the stereotypic disease of "displaced children") and its next-of-kin, marasmus.

At the population level, similar conundrums exist. Our traditional recourse to blame it all on "balanced polymorphism" sounds increasingly more ludicrous by the day. The idea that a greater evolutionary advantage awaits those who do not first die from the fully expressed disease, increasingly sounds like apocrypha- or a lot of hokum. Does anyone seriously believe that nature would swap sickle cell anemia- even in its heterozygous "carrier" state- for falciparum malaria? We still do not understand why familial mediterranean fever is common amongst Shephardic Jews, Gaucher's and Tay-Sach's disease in the Ashkenazi, Behcet's eponymously-named disease amongst the Lebanese, alpha thalassemia in mainland Chinese, cystic fibrosis in the Swedes and congenital nephrotic syndrome amongst the Finns. A full understanding of plagues, both ancient and modern, relies on social history, old-fashioned detective work, sophisticated DNA gadgetry, and a more humble reappraisal of human behavior. The scourge of syphilis, which followed the returning conquistadors from the New World, bubonic plague amidst the Dickensonian squalor of Europe, epidemic tuberculosis amongst the isolated Eskimos, lead poisoning in the sprawling ghettoes of the industrial age, and more recently, the HIV pandemic are best understood within that social construct.

As another wise old man recently informed me with respect to the raging health care debate, "You can't fix health care until you fix folks". Maybe, I'm just being naive, but I think he has a point.

As always, I see you again Friday lunch-time, at the CME lounge.

Beze Adogu, MD, Ph.D, FACP



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SHOULD WE RETIRE CPR?

In a provocative editorial, Gust Bardy, *N Engl J Medicine*, 2011, forcefully outlines the case against CPR: its real-world therapeutic value remains unproven; despite its ever-expanding use, outcomes following out-of-hospital cardiac arrest have largely remained unaltered; any putative benefits attributed to CPR are more likely a consequence of the earlier deployment of defibrillator therapy; autopsy data reveal serious iatrogenic organ and tissue damage following CPR in survivors; and, if compression-only CPR works just as well as full compression-ventilation CPR, possibly no CPR could be equivalent to compression-only CPR? Almost as an aside, he observes that CPR merely subsidizes the cardiac "not-for-profit" world. He points out that cardiac rhythms degenerate rapidly, and within 25 minutes, all patients with cardiac arrest are in asystole. You may not agree with him, but at least you ought to listen to his brief for the prosecution.

DIGOXIN USE IN ESRD

Finally, a study appears to nail the poor prognostic outcomes associated with digoxin treatment in dialysis patients. This, after the controversy (and muddied waters) resulting from the DIG trial, the PACES study (kidney failure sub-group analysis) and countless case reports. Chan et al, *J Am Soc Nephrol*, 2010 studied survival amongst 120,864 hemodialysis patients, which demonstrated that digoxin use was associated with a 28% increased risk of death during the study beriod. Other notable associations with heightened mortality include high serum digoxin levels, low dialysate K prescription and low pre-dialysis serum K levels. Can we all finally stop using digoxin in dialysis patients?

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ANTIBIOTICS FOR ACUTE OTITIS MEDIA

Worried mothers and stoic pediatricians have long battled over the use of antibiotics for pediatric infections through the ages. The battle-lines just got shifted again. In a recent study of childhood otitis media in those under 2 years of age, Huberman et al, *N Engl J Medicine*, 2011, provide evidence that antibiotics (amoxicillin-clavulanate) reduce time to resolution of symptoms and (objective) signs of inflammation as seen on otoscopy; even more remarkably, antibiotics reduce overall symptom burden in sufferers. However, this is at the cost of diarrhea (in 25-50% of children) and a high risk of diaper dermatitis. I guess this makes it 1-0 for all sick-by-proxy mothers everywhere.

GUIDELINES SHOULD GUIDE, NOT DECIDE

When ex-President George W. Bush declared that he was the "Decider", little did we suspect he was on to something profound. It now appears that guidelines- even those published by such eminent groups as the Infectious Diseases Society- are, well, only guidelines. Lee & Vielemeyer, *Arch Intern Medicine* 2011, put the guidelines of the Infectious Diseases Society to the test: 55% of the recommendations were based on expert opinion or clinical anecdote, the lowest level of clinical certitude. Equally, for the platinum-grade "level A recommendations", 37% were also based on expert opinion. The vast majority of those guidelines were based on level II (non-randomized trials or observational studies) and level III (case studies/reports or expert opinion) data, and even more telling, guidelines were (on average) 6.7 years out of date. Of course, guidelines are useful aides in clinical management, but do not supersede critical thinking focused on the specific patient at hand. Each astute clinician is the "Decider". Medical residents, beware!.

ENDING THE CYCLE OF INTESTINAL VIOLENCE

Antibiotic-associated (C. difficile) entero-colitis is common, has become even more common, and is still associated with high levels of morbidity. Metronidazole and Vancomycin are both useful and effective therapy, but are associated with relatively high post-treatment recurrence rates. A 10-day course of oral Fidaxomicin has been reported by Louie et al, *N England J Medicine*, 2011, to have similar cure rates as oral Vancomycin, but virtually halves recurrence rates over 4 weeks. The underlying reason for this bonus effect is unclear, but could relate to an improved (though partial) preservation of normal intestinal flora with oral Fidaxomicin.

GERIATRIC FRAILTY SYNDROME

Geriatric frailty is the phenotypic expression of heightened vulnerability in the elderly, leading to death within a median time of 2 years after diagnosis (Fried & Tanger, *J Gerontology*, 2001). Described as an "extreme phenotype of aging", frailty is not strictly age-dependent, though its prevalence increases with advanced age, rising from 3-7% in the 65-75 y.o. age group to over 22% in patients over 75 y.o. Geriatric frailty syndrome is a slowly developing illness which identifies patients at higher risk for poor medical outcomes and death, and the underlying theme is both progressive physiologic decline, loss of functional reserve and higher susceptibility to other diseases, infections, falls, hospitalization, institutionalization and death. Such patients prove intolerant of physiologic or psychologic stress. The full syndromic expression is typically initiated by lack of activity or concurrent disability, new disease onset (such as infections, organ failure, acute injury), stress, impaired nutritional intake and organ dysfunction.

Clinical diagnosis as proposed by Fried et al, *J Am Geriatr Soc*, 2006, relies on demonstrating 3 out of 5 defining attributes: unintentional weight loss >10% body weight; self-reported exhaustion; generalized fatigue as assessed by poor hand-grip strength; slow walking speed; low levels of physical activity. Those that have only 1 or 2 attributes are described as "pre-frail", underlying a high-risk group who are still amenable to early clinical reversal.

The cause(s) of frailty are unknown, but are thought to include age-related attrition, biologically-determined cellular senescence, long-standing inflammatory changes, hormonal deficits, glucose intolerance, chronic anemia, reduced nutritional intake (either from anorexia, nausea, poor utilization or malabsorbtion) and clinical depression. Associated serologic markers include low levels of sex hormones (including androgens, such as dehydroepiandrosterone sulfate), insulin-like growth factor-1, growth hormone, vitamin D and cholesterol; conversely, there is evidence of activated inflammatory and clotting cascades as well as glucose intolerance, manifest as increased levels of leucocytosis, hemoglobin A1c, IL-6, C-reactive peptide, factor VIII, fibrinogen, D-dimers and circulating plasma insulin.

Treatment should be based on early identification of "high risk" patients (ideally, whilst still in the pre-frailty stage), and where possible, early reversal of risk factors. Predictors of frailty as identified by Ravaglia et al, Age Ageing, 2008, include male gender, age >80 years, calf circumference <31 cm, disabilities involving ADL (activities of daily living), poor gait/balance test scores, physical inactivity, polypharmacy as defined by regular use of >3 drugs, sensory deficits on neurologic evaluation, and pessimism concerning long-term health outcomes. Nutritional intake should be optimized, using appetite stimulants when necessary. Resistance training and low-level exercise should be adopted, tailored to the specific situation of individual patients. Symptomatic remedies for underlying complaints must avoid drug-drug and drug-disease interactions, whilst hormonal supplements are best reserved for cases of proven deficiencies. Anemia should be treated based on putative cause, and support provided for care-givers and family members.

IS PAD AN INFECTIOUS DISEASE?

Peripheral artery disease (PAD) is common, multi-systemic, afflicting 8.2% of the general population (Carmelli et al, *Am J Epidemiol*, 2000) and manifesting chiefly as intermittent claudication ("lower limb effort angina of walking"). PAD is a powerful predictor of ischemic events elsewhere, particularly in the heart and brain (Criqui et al, *N Engl J Medicine*, 1992). Familial studies suggest that the contribution of inheritable traits towards the predisposition to PAD is less than 22% (Kullo et al, *Atherosclerosis*, 2006; Murabito et al, *Am J Epidemiol*, 2006). The major non-inheritable risk factors for PAD are chronic arterial hypertension, diabetes mellitus, smoking and hyperlipidemia, though the predictive potency of each risk factor depends on the specific arterial bed involved (Brevetti et al, *Circulation*, 2010). Though vascular inflammatory changes had been noted histologically from the earliest descriptions of atherosclerosis by Virchow (Virchow, Cellular Pathology, 1858), its pathogenetic role in atherogenesis has only recently become explicit (Libby et al, *Circulation*, 2002). The consensus is that cytokines and other inflammatory markers are not mere bye-standers or residua of atherogenic plaque formation, but are the actual initiators of atherogenesis (Braunersreuther et al, *Thrombosis Hemostasis*, 2007). Serologic studies indicate some linkage between PAD and prior infections with Helicobacter pylori, CMV and chlamydiae pneumoniae (Bloemenkamp et al, *Atherosclerosis*, 2002); atherogenecity from infections appears to be linked to the inflammatory response (as measured by post-infection CRP titers), female sex and recurrence of infections. However, associationship does not infer causality: the data actually shows a stronger link to CRP (as index of inflammation) than any specific infection(s); antibiotics have not been shown to reduce PAD risk; and certain defined risk factors (such as smoking) are also independently associated with infections (such as chlamydia pneumoniae bronchitis) suggesting that seropositive anti-chlamydial antibody titers might only represent a surrogate for chronic smoking, or perhaps, COPD.

VITAMIN D DEFICIENCY

Vitamin D, a secosterol vitamin, exists in 5 molecular forms; vitamin D2 (ergocalciferol) is primarily of plant origin, and vitamin D3 (cholecalciferol) is of animal origin. Human stores are 85% derived from skin synthesis (under UV light) and 15% derived from dietary sources, undergoing serial dual hydroxylation at both the liver (to form 25-hydroxy vitamin D) and kidneys (to form 1,25-dihydroxy vitamin D) as its fully bioactive form. The vitamin D receptor forms a molecular complex with active vitamin D (substrate) and the retinoid X receptor (co-factor), attaching to cellular DNA to alter gene expression. Vitamin D deficiency is defined as serum 25-hydroxy vitamin D levels <30 ng/mL. Each 100 IU of oral vitamin D increases serum 25-hydroxy vitamin D by 1 ng/mL. Vitamin D deficiency is associated with increased intracellular calcium and renin activation (activated vitamin D suppresses the renin promoter gene, leading to low plasma renin activity), resulting in vasoreactivity and systolic hypertension; decreased expression of the insulin receptor (resulting in insulin resistance and diabetogenesis); vascular calcification; secondary hyperparathyroidism; dyslipidemia and congestive cardiac failure (Vanga et al, *Am J Cardiol*, 2010).

ANTI-HIV THERAPY & ACUTE MI

HIV is not uncommon, whilst coronary artery disease/acute MI is common in America. Not surprisingly, there is a recognized intersection between the 2, with HIV infection associated with a 75% increase in acute MI rates. A recent ICU consultation request revealed a young adult HIV-positive male with HAART-related proximal tubulopathy and Fanconi syndrome in the context of chronic kidney disease. A review of this clinical association led to a case-control study by Lang et al, *Arch Intern Medicine*, 2010, showing that initiation (but not long-term use) of abacavir treatment, long-term treatment with nucleoside reverse transcriptase inhibitors (NRTI: zidovudine and stavudine), protease inhibitors (except saquinavir) were all associated with higher odds of suffering an acute MI in HIV-positive patients. However, use of non-nucleoside reverse transcriptase inhibitors (NNRTI: efavirenz, nevirapine) and saquinavir appeared to be safe.

CATHFLO A WEEK, KEEPS THE DOCTOR AWAY

A small study published by Hemmelgarn et al, *N Engl J Medicine*, 2011 for the PreCLOT Study Group randomized 225 hemodialysis patients to either conventional "packing" of dialysis catheters with 5000 units heparin/mL or once-weekly recombinant tissue plasminogen activator (rt-PA) using 1 mg/catheter port. The rt-PA arm did substantially better: 45% fewer catheter malfunctions, 3x fewer bacteremic episodes, though at substantially higher cost (which was more than offset by the prevention of possible sepsis). As vascular access has been the proverbial "Achilles Heel" of chronic hemodialysis care, this might prove to be 1 more arrow in our arsenal.

SEVERE HYPOGLYCEMIA IN DIABETIC PATIENTS

Hypoglycemia is 1 of the most common complications of diabetes management. Risk factors for hypoglycemia include chronic alcoholism; inappropriate increase in insulin doses (based on spuriously elevated glycosylated hemoglobin level: HgbA1c can be elevated in hemoglobinopathies [where HbF is misread as HbA1c, as most commonly occurs in thalassemia], and also in hypertriglyceridemia, early pregnancy, iron deficiency and post-splenectomy states); oral hypoglycemic drug treatment (this is particularly true for long-acting sulfonylurea drugs, especially Glyburide: van Staa et al, *J Clin Epidemiol*, 1997); advanced age (Shorr et al, *J Am Geriatr Soc*, 1996); chronic renal disease (multiple factors suggested for hypoglycemia in CKD include extended elimination half-lives for oral hypoglycemic drugs, reduced renal gluconeogenesis, impaired caloric intake, loss of renal "insulinase" activity and impaired serum anti-insulin activity); liver dysfunction; concurrent illness/sepsis (including adrenal failure, hypothyroidism, celiac disease, gastroparesis/malabsorption syndromes and psychiatric/factitious illness all of which may first present as "recurrent hypoglycemia"); polypharmacy (with hypoglycemic drugs, including those not universally recognized as such, e.g. Tylenol, octreotide, interferon beta-12b, morphine, ASA/NSAIDs, beta-blockers, Chantix and theophylline).

ARCHIVAL WISDOM: FLUID RESTRICTION IN DIALYSIS PATIENTS

A dated reminder from Tomson CRV, *Nephrol Dial Transplant*, 2001, provides summary evidence that water restriction without salt restriction is neither supported by objective data nor scientific evidence. Without sodium, water redistributes throughout total body water and not only within the extracellular compartment, therefore limiting its impact on blood pressure. Also, the dipsogenic drive is reduced by dietary salt limitation (Rigby-Mathews et al, *J Am Soc Nephrol*, 1999) and is also modifiable with ACE inhibitor therapy (Oldenburg et al, *British Med J*, 1988) and avoidance of incident hypovolemia.

FAILURE OF NITRIC OXIDE IN SICKLE CRISIS

Gladwin et al, *JAMA*, 2011, report the failure of inhaled nitric oxide as treatment in acute sickle cell vaso-occlusive crises. Despite its promising antecedents in laboratory mice models as well as multiple case reports, any projected therapeutic use of nitric oxide collapsed in this double-blind, randomized, placebo-controlled multi-center trial. Looks like we are back to partial exchange blood transfusion. *Nunc dimittis*, I say, *nunc dimittis*.

ACETAMINOPHEN FOR CRUSH INJURY: WHO COULD HAVE THOUGHT THAT?

Boutaud et al, *Proc Natl Acad Sci*, 2010, report that therapeutic levels of acetaminophen can protect the kidneys from rhabdomyolysis-induced renal failure following crush injury in rats. Cell damage following trauma (or disease) triggers the release of heme proteins (such as myoglobin in muscles, and hemoglobin in red blood cells) which in turn help generate free radical species, leading to oxidative damage through lipid peroxidation. The lipid peroxidation cascade is apparently inhibited by acetaminophen, which acts to maintain heme-iron in the reduced ferric state rather than ferryl-iron. Acute kidney injury is therefore prevented.

DIFFERENTIATING METABOLIC ACIDOSIS

Metabolic acidosis can be usefully classified into 3 pathologic groupings: (1) Anion-Gap Metabolic Acidosis, remembered through the time-worn mnemonic "AT MUDPILES" (alcohols, toluene, methanol, uremia, diabetic ketoacidosis, pyroglutamate acidosis [acetaminophen], iron, lactic acidosis, ethanol, salicylates [watch for associated respiratory alkalosis]); (2) Hyperchloridemic Metabolic Acidosis with Hypokalemia (from GI losses typically as a result of intestinal/biliary fistulae, pancreatic fistulae, diarrheal diseases and ureterosigmoidostomy, as well as types I and II renal tubular acidosis); (3) Hyperchloridemic Metabolic Acidosis with Normokalemia/Hyperkalemia (adrenal failure, type IV renal tubular acidosis, pseudoaldosteronism types I and II, CKD stages III-V, exogenous therapy with acids, medications [heparin, K-sparing diuretics, Bactrim, NSAIDs, Cyclosporine])

DEPARTMENT OF NEW DRUGS: DABIGATRAN

Coumadin, the prototypical vitamin K antagonist, is of proven benefit as therapy and prophylactic regimen in thrombo-embolic disorders. However, its clinical effect is delayed (after an initial pro-coagulant phase which actually increases the risk of thrombo-embolism), it has multiple drug-drug and drug-food interactions, potency is variable based on genetic polymorphisms involving cytochrome P450 2C9 system, and dosing reliance on frequent laboratory monitoring of INR makes its routine use complicated and costly. Therefore, as demonstrated by Connolly et al, *Circulation*, 2008, Coumadin use is associated with a low acceptance rate, a high default rate (amongst patients) and inefficient therapeutic goals (typically, patients are within therapeutic range only 50-60% of the entire duration of treatment).

Into that breach steps in Dabigatran (Pradaxa), an oral non-protein DTI (direct thrombin inhibitor) which is administered as a pro-drug and has few notable interactions with either drugs or food. Administered as 150 mg p.o. BID, it is rapidly absorbed, attains peak plasma levels within 2 hours of dosing, being 35% protein bound and 80% excreted by kidneys. It is equivalent or superior to Coumadin at such doses in preventing embolic events in atrial fibrillation, and has an equivalent or lower risk for major bleeding episodes (Connolly et al, N Engl J Medicine, 2009). Similar findings were reported for venous thrombosis (Schulman et al, *N Engl J Medicine*, 2009). Only 50% of the dose (75 mg p.o. BID) is recommended for patients with GFR under 30 mL/min, and should be avoided in stage V CKD. As Pradaxa is a substrate for the P-glycoprotein efflux transporter, plasma drug levels can vary by up to 67% with either inducers (such as rifampin, which reduce plasma levels of Pradaxa) or inhibitors (such as amiodarone, which increase plasma levels of Pradaxa). It is therefore prudent to avoid other drugs that affect the P-glycoprotein efflux pump. With the exception of dyspepsia, all side effects are less common with Pradaxa in comparison to Coumadin.

OF MICE AND (WO)MEN

In a paper from San Francisco, Bullard et al, *Surgery*, 2010, provide evidence that in health and in disease, women do rule! Female animals are more tolerant of trauma as well as extreme blood loss than male animals, and the organ-protective effects are traceable to rapidly-triggered non-genomic effects of estrogens in response to tissue damage. This protection is lost in post-ovariectomy states, but is readily replaced with exogenous estrogen administration. In the ICU, a parallel observation is the better outcome observed in women following sepsis, injury and blood loss when compared to their male peers. The authors suggest that for improved survival, men ought to be more like women. Enough said.

REHASHING THE PERILS OF SMOKING

Smoking is the #1 preventable cause of death in America. Smoking as neuroprotective strategy had been touted in the past following reports of a negative association between smoking and Parkinson's disease. A new study from Rusanen et al, *Arch Intern Medicine*, 2011, demonstrates that heavy smoking in mid-life was associated with a doubling of the risk for dementia, both Alzheimer's disease as well as vascular dementia. A quick reminder of the diseases thought to show a (weak) negative association with smoking: aphthous stomatitis and oral ulcers (Tuzun et al, *Int J Dermatol*, 2000); ulcerative colitis (Pullan, *Ann Royal Coll Surg*, 1999); Parkinson's disease (Gorell et al, *Neurology*, 1999); endometrial cancer/endometriosis and uterine fibroids (Lesko et al, *N Engl J Medicine*, 1985); pre-eclampsia (Klonoff-Cohen et al, *Obstetr Gynecol*, 1993), and possibly, thyroid cancer in women. For each death prevented by avoiding any 1 of the listed diseases, smoking causes 100 other deaths via other pathways.

TIMELY REMINDER: PROPER USE OF D-DIMER TEST

Pulmonary embolism is a potentially fatal condition, and ought to be considered in any patient presenting with acute shortness of breath. Whilst clinical confirmation of probable pulmonary embolism is a worthy goal, it can be a costly, time-intensive and technologically-demanding procedure involving contrast exposure as well as multiple radiologic images. Therefore, it is important to quickly and safely exclude PE in the 30% of cases who are dually-negative based on pre-test probability of PE <20% plus normal D-dimer levels. If both are negative, it is not PE. The rest will require V/Q scans or CT scans to confidently exclude PE. Remember that D-dimer elevation is very non-specific, being found in any condition associated with increased fibrin generation as well as in CKD (Karami-Djurabi et al, *Am J Medicine*, 2009). Moral: D-dimers cannot be used for making a diagnosis of PE, but to exclude that diagnosis.