Athens Kidney Center
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RETURN SERVICE REQUESTED

H. PYLORI TRACKS WITH HIGH GLYCEMIC LEVELS

Chen et al, *J Infect Dis*, 2012, report that high BMI was synergistic with the presence of gastric *Helicobacter pylori*, the effect surpassing the sum of each individual risk factor, in increasing hemoglobin A1c levels. Utilizing a cross-sectional analysis of NHANES data for H. *pylori* status, hemoglobin A1c levels, lifestyle factors and other demographic information, the investigators discovered that positive H. pylori status was associated with higher mean hemoglobin A1c levels in those over 18 y.o., a feature that persisted even after excluding diabetics or those on hypoglycemic therapy. A similar relationship was noted for hemoglobin A1c and higher BMI levels. The significance of this single study is that detection and treatment of H. *pylori* might become a cardinal feature of glycemic control in diabetics, and could possibly help explain the prevalence of gastro-intestinal symptoms in poorly-controlled/brittle diabetics including DKA.

BEWARE ACUTE KIDNEY FAILURE IN CHILDREN

Mammen et al, *Am J Kidney Dis*, 2012, prospectively analyzed data on 126 children hospitalized with acute kidney injury in a pediatric ICU in Canada. Most cases of AKI were associated with open heart surgery; about a quarter of AKI cases were in neonates. Using the recent AKI Network classification, 35% of AKI cases were stage 1, 37% were stage 2 and 28% were stage 3. Children were followed up for 1-3 years. At least, 10% of all cases had developed chronic kidney disease (defined as persistent albuminuria or GFR <60 mL/min) on follow-up: 10.6% of those patients with stage 1 AKI, 10.6% of stage 2, and 17.1% of stage 3 AKI. An additional 46.8% of AKI survivors were at high risk for later CKD, based on findings of reduced GFR (between 60-90 mL/min), presence of chronic arterial hypertension or evidence of glomerular hyperfiltration. Therefore, about 60% of childhood AKI survivors would soon develop chronic kidney failure or were found to be at high risk for same.

STOCK MARKET CRASHES & CARDIAC DEATH: NOT

Previous studies have linked excessive cardiac deaths to stressful events such as earthquakes, soccer matches and incoming missile offensives. What could, therefore, be more potent a trigger for cardiac demise than the October 2008 stock market crash? Schwartz et al, *Am J Cardiol*, 2012, set out to investigate this link using raw stock market data from the Dow Jones Industrial Average Index, Los Angeles county death certificates and annualized population rates for Los Angeles over 4 years. They found marked seasonal variability in total as well as cardiac deaths, with higher deaths in winter months (17% increase in total deaths, 24% increase in circulatory deaths, 28% increase in coronary cardiac deaths and 38% increase in MI deaths). After adjusting for seasonal variations in death rates, the stock market crash did not appear to affect death rates in Los Angeles. Indeed, deaths from coronary heart disease have been slowly declining since 1985.

SUMMARY OF BREAST CANCER SCREENING IN NORWAY

Breast cancer has been highlighted as a potentially "preventable" disease. Prevention, however, mostly hinges on early detection and treatment, which itself is dependent on appropriate screening. Proper scientific evaluation of screening programs are notoriously difficult to ascertain, in part because those must be compared to detection rates in the absence of screening, as well as "lead time" where mammographic diagnosis precedes clinical diagnosis. Since 2005, all Norwegian females aged 50-70 years are routinely invited for mammography, as part of a national screening program, every 2 years. Using this novel effort, Kalager et al, *Ann Intern Med*, 2012, compared both previous (historical) temporal trends and trends within still-unscreened geographical populations in Norway with results obtained through the current population-wide screening efforts which have enjoyed a high degree of compliance. The researchers estimate that 15-25% of breast cancers diagnosed through this screening program would never have become clinically apparent. They surmise that for every 2,500 women screened in this program, 20 cases of breast cancer were found and treated early, preventing 1 death from breast cancer, at the cost of 6-10 women who are over-diagnosed with cancer.

the SECOND OPINION

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FROM THE EDITOR

For decades, perhaps over a century or so, chronic arterial hypertension has posed as both enigma and Holy Grail. Scores of gifted investigators over the ages have dedicated their careers to disentangling the nature of elevated blood pressures. There has been some progress, earned at the price of personal frustration and reflective humility for those at the forefront of hypertension research, but we are often chagrined to admit that the future has not yet come. For one, we still do not fully understand the nature- or causes- of primary arterial hypertension, which we call "essential", meaning idiopathic or of unknown causation. For a very long time, conventional medical opinion held that an elevated blood pressure was all to the good, serving to perfuse distant organs and working with a singular purpose to support cardiac load. Indeed, no less an authority- I almost prefaced that with the word "medieval", but this was only in 1931- as John Hay, MD, had declared that "the greatest danger to a man with high blood pressure lies in [its] discovery, because then some fool is certain to try and reduce it". It is no wonder then, that the President of these United States, Franklin Roosevelt, was left largely untreated and unattended at death's door, despite ravaging blood pressures said to have exceeded 300/190 mmHg!

With time, but that was several decades later, tentative therapies for chronic hypertension were serially introduced, ranging from the ineffective to the mediocre. Such historical stand-outs include injections with typhoid bacilli, in the pious hope, one assumes, that God might send you either lice or send you fleas at death's door, but was unlikely to send you both- an arcane philosophy that gave us, amongst others, Occam's razor, or the concept of diagnostic parsimony. This was followed by other therapies such as the anti-malarial, pentaquine, the insipid (and deservedly infamous) Kempner rice diet, dubious herbal concoctions containing rauwolfia alkaloids (the forerunner of that great hemodynamic straight-jacket, reserpine), and a host of autonomic neurone blockers. Patients referred for anti-hypertensive treatment were pretty much like today's cancer- or renal- patients on chemotherapy: very much alive, but generally in poor shape. Surgical sympathectomy fleetingly assumed the status of accepted standard of care, sacrificing orthostatic competence for avoidance of predictable end-organ damage. Recipients of surgical denervation were bed-bound for the rest of their days- or until disease recrudesced- a pastel daguerreotype of premorbid vitality and strength. Initial procedures were variations on the theme of ventral rhizotomy, with the surgical interruption of the lower six thoracic and upper two lumbar anterior spinal nerve roots, but with time and growing confidence, came total splanchnic nerve resection, celiac gangliectomy, and ablation of the greater splanchnic nerves. Not surprisingly, surgeries, surgeons and patient outcomes were all equally bloody.

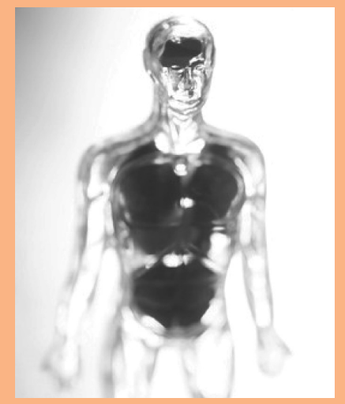
Fast forward 60 years from then: using catheter-delivered radio-frequency ablation, a gritty vascular procedure which has already received "honorable mention" in many dispatches from the war-fields of complex ventricular arrhythmias, nerve disruption at the renal artery level is now back on prime time. Patients with drug-refractory arterial hypertension are presently enrolling in the Symplicity HTN-3 Trial, which promises to advance the use of renal denervation as treatment for drug-resistant hypertension. It is with bated breath that we slowly walk our way back to the Past as Future. As the poet remarked, If you look forward enough, you'd see the past more vividly. Welcome to our future in hypertension research.

As always, I'll see you Friday lunch-time, at the CME lounge. Beze Adogu, MD, PhD, FACP

Beze Adogu, MD, Ph.D, FACP

IT'S SUMMER, IT'S HOT AND KIDNEYS ARE PRONE TO BUST

Data from New York's Center for Environmental Health confirm that high summer temperatures increase the risk of acute kidney injury (AKI) as well as hospitalizations for kidney stones, UTIs and multiple lower urinary tract diseases. In a case-crossover design used to study a total of 147,885 New York State hospitalizations with a renal diagnosis, Fletcher et al, *Am J Epidemiol*, 2012, show that the risk of hospitalization for AKI increased by 9% for each 5 degrees F increase in mean environmental temperature. That risk was greatest for the poor, young (aged 25-44 years), Blacks and Hispanics. For each 5 degrees F increase in ambient temperature, young adults aged 25-44 years had a 18% higher risk of AKI compared to older folks (aged 45-64 years), those in the lowest income quartile (earning $31,406 per annum or less) had a 13% higher risk in comparison to those in the highest income quartile (earning $55,869 per annum or more), whilst Hispanics had a 20% higher risk of AKI compared to non-Hispanics, Blacks had a 14% higher risk compared to Whites, and Asians had a 12% lower risk compared to Whites. Those associationships appeared to be greater in urban compared to rural counties.



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IF YOU MUST HAVE AN ST-SEGMENT ELEVATION MI (IN FRANCE, AT LEAST).....

Belle et al, *Am J Med*, 2012, compare outcomes following ST-segment acute myocardial infarction in academic and non-academic medical centers in France. They analyzed data from a prospective study of 3,059 patients enrolled at 39 academic and 183 non-academic medical centers in France. Unadjusted 1-year mortality for ST-elevation MI was 10% vs 15% in those treated at academic and non-academic hospitals, respectively. For non-STEMI, the 1-year mortality was 13% at academic centers and 14% at non-academic centers. In non-academic medical centers, having percutaneous coronary intervention (PCI) capabilities was closely associated with adoption of recommended re-perfusion therapeutic protocols and closer adherence to accepted coronary treatment guidelines, as was generally the case in academic medical centers. After adjusting for baseline characteristics, the risk of death at a non-academic hospital relative to an academic center was 1.13 (if PCI technology was available) and 1.65 (if there was no PCI capability) for ST-segment elevation MI. For those with non-STEMI, relative death risk in comparison to academic centers was 0.95 (in non-academic hospitals with PCI capability) and 1.06 (without PCI capability). In this study, the importance of guidelines-adherence in academic medical centers confers a huge survival advantage in acute MIs.

PREDICTION OF HYPERKALEMIA IN CARDIO-RENAL SYNDROME

Cardio-renal syndrome is common and associated with a high incidence of mortality and morbidity, often predicted by findings of persistent hyperkalemia. Hyperkalemia reflects failure of potassium homeostasis as a result of advanced age, kidney dysfunction, glycemia-related ionic fluxes and hypo-renin hypo-aldosteronic syndromes (either from medications, distal tubular dysfunction or systemic disease) commonly referred to as type 4 renal tubular acidosis. Jain et al, *Am J Cardiol*, 2012, in a retrospective analysis using a logistic regression model, analyzed 15,803 patients cardiac patients for risk factors that may predict hyperkalemia. Almost a quarter of study participants developed hyperkalemia, which was associated with a doubling of the risk of death and a 50% higher risk of hospitalization. Hyperkalemia was predicted by severity of CKD, presence of diabetes mellitus, history of coronary artery disease/ischemic cardiomyopathy and presence of peripheral vascular disease.

WHY ARE PHYSICIANS SO DIFFERENT: RE-EXAMINING CT USE AMONGST ED DOCS

Standard of care is a moving target: it all depends on your perspective and vantage point. Clinical assessment by (presumably) equally well-trained physicians is so different, that one suspects it must be a huge driver for cost and outcomes differentials. Prevedello et al, *Am J Med*, 2012, report on variations in CT orders for non-traumatic headaches by ED physicians at the Brigham & Women's. In a cross-sectional study of 55,286 ED encounters, 8.9% ultimately led to a head CT exam. The variation in CT orders for non-traumatic headaches ranged from 15.2% to 61.7% per physician, and 4.4% to 16.9% for all ED encounters overall- a grossly divergent use which apparently persisted even after controlling for important clinical (and institutional) variables. The next stage of this study should focus on what actually drives physician utilization: Fear of malpractice claims? Perseverating insistence on diagnostic certainty? Availability of resources? Ignorance of cost-benefit analyses? Patient demographics? Diurnal periodicity? Ability to complete competent (neurologic) examinations at the bedside? Training and/or experience? Fear of peer disapproval? Paranoia?

NO KIDDING: SLEEPING PILLS COULD KILL YOU

We are an insomniac nation: 6-12% of all Americans use a sleeping pill each year. Yet, as amply demonstrated by Kripke et al, *BMJ Open*, 2012, that common practice is associated with increased mortality risk. Using longitudinal data from the electronic health records of Geisinger Health System, America's largest integrated rural health system, 10,529 patients who received prescriptions for hypnotic pills from 2002 to 2007 were matched to 23,676 controls who did not receive similar prescriptions. After adjusting for confounders and co-morbidities, the investigators established a substantially higher risk of death amongst the pill-takers on hypnotic agents. There was a robust dose-response relationship between hypnotic doses prescribed per year and relative hazard of death amongst pill-takers. Kripke et al conclude that though this strong relationship does not necessarily prove causality, using hypnotic pills more than tripled the risk of death even amongst those taking less than 18 pills each year, and estimate that up to 507,000 excess deaths in the United States could be legitimately laid at the doorsteps of hypnotic use.

THE END OF OBESITY: ARE FAT TRENDS FINALLY THINNING OUT?

Obesity is a modern epidemic: 30-plus percent of most demographic groups in most states are obese. In an encouraging study by Flegal et al, *JAMA*, 2010, obesity trends in the United States culled from the NHANES data-base from 1999-2008, we examined. Obesity was defined as BMI >30 kg/m2 and overweight as BMI of 25-29.9 kg.m2. Age-adjusted prevalence of obesity was 33.8% overall, 35.5% for women and 31.6% for men. Obesity was most common amongst the over-40's in age. Interestingly, there was no significant increase in obesity amongst women from 1999 to 2008 but did show a linear progression among men. The authors conclude that whilst we are still an Obese Nation, the rate of increase may finally be leveling off, as social and physical risk factors for obesity come under continuous challenge. They recommend the complementary efforts of healthy eating, clinical prevention and evidence-based treatment strategies in tackling this modern epidemic.

NODDING IN SUDAN: MASS HYSTERIA OR NEW ENTITY?

An outbreak of apparently unprovoked clusters of nodding with seizure activity has been reported from the newly-independent nation of South Sudan (Wadman, *Nature*, 2011). This bizarre neurologic condition is characterized by repetitive nodding attacks, convulsive seizures and motionless staring, mostly in young children aged 5 to 15 years within fairly loose geographic clusters. Initial studies indicate that affected children have a high prevalence of onchocerciasis (river blindness) in some but not all clusters. Most clusters do not appear to exhibit a gender bias, and physical examination of patients have been remarkable for the absence of focal neurologic deficits. Anecdotal reports suggest that a minority of cases may progress to an encephalopathic picture with inanition and eventual demise. So far, there has not been a report of spontaneous or induced recovery from this syndrome. Candidate etiologic factors in nodding syndrome include viral/prion brain infection, neurotoxin exposure (possibly related to the internecine East African conflicts?), avitaminoses or other nutritional deficiencies, autoimmune disease or psychogenic factors. Some investigators have noted superficial similarities to other tropical diseases as disparate as kuru, tropical ataxic neuropathy, and less convincingly, "vanishing testes syndrome".

INTENSIVE GLUCOSE CONTROL: WHAT WE HAVE LEARNT

We always knew that microvascular complications of type 2 diabetes (i.e. neuropathy, retinopathy and nephropathy) were linked to poor glycemic control; conversely, intensive glycemic control prevents those complications (DCCT Research Group, *N Engl J Med*, 1993) though at the considerable cost of 22% increased mortality in the ACCORD trial (Gerstein et al, *N Engl J Med*, 2008). A meta-analysis by Coca et al, *Arch Intern Med*, 2012 confirms that intensive glycemic control (defined as hemoglobin A1c <7%) reduces the rate of micro- and macro-proteinuria but not "clinical outcomes" defined as death from kidney disease, doubling of serum creatinine levels or initiation of dialysis for ESRD. Coca et al rightfully acknowledge that we cannot explain these findings, and point out the problems in cross-study comparisons: (1) outcomes were particularly good, even amongst study participants on "routine" glycemic control; (2) the benefits of intensive glycemic control may be blunted if therapy is started too late, for relatively short periods or not aggressively enough (perhaps, to "normal" hemoglobin A1c levels); (3) differences amongst groups may be too subtle to detect in the absence of huge numbers of enrolled participants; (4) perhaps, the most likely reason, being a "ceiling effect", whereby further serial reductions in hemoglobin A1c levels bring about increasingly less "bang for its [metabolic] buck". In general, it appears that in type 2 diabetes mellitus, emphasis should *jointly* be on control of associated (metabolic) co-morbidities, *reasonable* glycemic control (hemoglobin A1c <7.5%) based on age and metabolic tolerance, and focus on the high prevalence of early cardiovascular death.

DIABETIC NEUROPATHY: NEW DRUGS, OLD FRUSTRATIONS

Diabetic neuropathy is common and disabling, impacting the quality of life in up to 50% of diabetics. The cost of diabetic neuropathy is estimated at $10.9 billion per year, with prescription pain pills alone costing ~$1300 per patient per year. No treatment works for all patients, all the time; the astute doctor would try different remedies whilst encouraging the patient to remain optimistic through frustrating interludes. Treatment strategies for diabetic neuropathy include:

1. Anti-depressants: Tricyclics have been the main-stay of therapy for decades despite their common anti-cholinergic adverse effects, as well as insomnia, hypomania and orthostatic dizziness. Commonly used agents are Impiramine or Desipramine or Amitriptyline, each commonly prescribed as 25-100 mg p.o. QHS, but Amitriptyline probably has the best evidence for efficacy. Lately, serotonin-norepinephrine reuptake inhibitors (SNRIs) have been introduced for diabetic neuropathy, typically either Duloxetine 60 mg p.o. QD-BID or Venlafaxine 75 mg p.o. QD-TID.
2. Anti-convulsants: several anticonvulsants are now employed for pain control as a ready substitute for anti-depressants, but each anti-convulsant also comes with a peculiar constellation of side-effects. Overall, evidence best supports the use of pregabalin and gabapentin, and to a lesser extent, valproic acid, for use against diabetic neuropathy in this class. Those anti-convulsants in common clinical use are: Pregabalin 100-200 mg p.o. TID; Topiramate 50-400 mg p.o. QD (beware of hypoglycemia and cognitive dysfunction); Lamotrigine 50-400 mg p.o. QD; Valproic acid (500 mg p.o. QD-BID (beware hepatotoxicity); Carbamazepine 200-600 mg p.o. BID; Lacosamide 50-400 mg p.o. QD (associated with diverse neurologic deficits suggesting cranial neuropathy and EKG changes simulating angina); Gabapentin 300-1200 mg p.o. TID (may cause sedation, ataxia and diarrhea).
3. Local anesthetics such as Capsaicin C cream 0.075% applied QID to affected areas or Lidocaine 5% patches applied up to thrice daily. The mechanisms of their action are thought to involve C-fiber stimulation with depletion of substance P for capsaicin, and blockade of neuronal sodium channels for lidocaine.
4. Opiates: Ultram 25-200 mg p.o. daily vs Oxycodone 20-100 mg p.o. daily vs Dextromethorphan 100-400 mg daily vs Morphine 7.5-100 mg daily; for each opiate, start (very) low and titrate upwards, and be aware of common side effects of nausea/vomiting, dry mouth, sedation/somnolence, constipation, pruritus, excessive fatigue and paradoxical insomnia.

5. Anti-arrhythmics: Mexiletine 675 mg daily

ANALGESIC PRESCRIPTION AFTER LOW-RISK PROCEDURES: AND THE BEAT GOES ON.....

Analgesia is commonly prescribed by doctors after procedures, including low-risk, short-stay/same-day interventions. What is still unknown is what happens to the vast majority of analgesic recipients after the procedure is concluded and wounds have healed. Alam et al, *Archives Intern Med*, 2012, are to be congratulated for this retrospective cohort study from Ontario, Canada. They identified 391,139 opioid-naive elderly patients who had recently undergone low-risk surgical intervention (e.g. cataract removal, laparoscopic cholecystectomy, vein stripping and transurethral prostatectomy), of whom opiates had been prescribed to 27,636 (7.7%) within 7 days of the procedure. At 1 year post-surgery, 30,145 (7.7%) of patients were still on opiate prescriptions. Oxycodone use had gone up from 5.4% within 7 days of surgery to 15.9% at 1 year after surgery. Therefore, patients receiving opiates following minor surgery were 44% more likely to become long-term opiate users within 1 year in comparison to those who did not receive any opiates. Similar trends were observed for NSAID use: 383,780 NSAID-naive patients who had undergone same low-risk procedures had NSAIDs prescribed to 1169 (0.3%) within 7 days of procedure, resulting in 30,080 (7.8%) still on NSAIDs exactly 1 year after: a 374% increase in NSAID use compared to those who were not prescribed NSAIDs within 7 days after surgery. So, doctor, next time you are tempted to just write pills for those who might not need analgesics, think 1 year down the road.....

PROBIOTICS & ANTIBIOTIC-ASSOCIATED COLITIS: WHERE IS THE EVIDENCE?

Probiotics, live microbes which consumption are thought to confer a significant health benefit (either given alone, or pre-mixed with non-digestible food items as prebiotics, which is thought to stimulate specific genera of colonic bacteria), is big business. The pathology of beneficence is equally clouded, though it is widely assumed to include specific micropathogen inhibition (via competition for nutrients, receptors or adherence factors), reduction of intra-colonic pH (which may be inhibitory to pathogens) and non-specific immune activation. Hempel et al, *JAMA*, 2012, provide a meta-analysis of the current literature, identifying 82 randomized controlled trials which typically used Lactobacillus [acidophilus/casei] as probiotic of choice (other genera include Bifidobacterium [lactis], Saccharomyces [boulardii], Streptococcus, Enterococcus and Bacillus). There was a statistically significant reduction in antibiotic-associated diarrhea following probiotic administration in the order of ~40%. The next step would identify those patients at greatest risk for diarrhea, those most amenable to probiotic intervention (perhaps, not ever in the immunocompromised), and which probiotic cocktail confers the most benefit.