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RETURN SERVICE REQUESTED

TRANSFUSING IN CARDIAC SURGERY

A restricted transfusion policy using 1 unit of packed RBCs at a time only for hematocrit <24% did not lead to inferior outcomes compared to a more liberal transfusion policy at hematocrit <30% amongst those undergoing elective cardiac surgery. The TRACS randomized controlled trial showed that there were no differences in the incidence of renal dysfunction, cardiogenic shock or ARDS amongst the 2 groups (Hajjar et al, *JAMA*, 2010). This restrictive transfusion policy was associated with lower costs, less wastage (of resources), more careful surgery, and not surprisingly, CMS is reviewing this finding with great interest....

METABOLIC ACIDOSIS

Metabolic acidosis is common in the ICU, often ignored, and predisposes the patient to added metabolic peril. An "average" adult generates approximately 1 mg/kg/day of titratable acid, usually from the metabolism of 4 g protein/kg/day. The kidneys are responsible for excreting the acid load, and acidosis is the result of reduced (renal) excretion capacity, increased acid generation (from protein intake or catabolism) or excessive alkali (bicarbonate) loss. Persistent acidosis results in a negative nitrogen balance with protein tissue degradation; myocardial dysfunction with sustained venoconstriction, pulmonary artery hypertension and prolonged hypoxemia; and accelerated bone demineralization (via heightened osteoclastic activity).

CATARACTS FOLLOWING ADT

Androgen deprivation therapy (ADT) is an accepted intervention in treating certain aggressive prostate cancers. Unfortunately, ADT is linked to future development of obesity, type 2 diabetes mellitus and cardiovascular disease. Now comes new data from Beebe-Dimmer et al, *Annals Epidemiology*, 2010, that ADT is also linked to a 9% higher risk of cataracts in male recipients.

THE FUTURE OF ANTI-AGING

Finally, there is evidence from mice that quiescent (aging somatic) cells can resume mitosis and reverse cellular degeneration through reactivation of telomerase enzyme (Jaskelioff et al, *Nature*, 2011). As you would no doubt recall from first-year biochemistry class, chromosomes (the nuclear condensation of genetic material within all dividing cells) are capped at each terminus by repeating DNA sequences called telomeres. With each mitotic division, there is a gradual erosion of telomeres (demonstrated as short telomere length), until it actually becomes too short to support further mitotic replication. It appears that this slow but inexorable decline in telomere length is the basis of cellular senescence and aging, and cells which have short telomeres can no longer divide, and ultimately die through apoptosis. However, the enzyme telomerase (which is really a terminal transferase catalyst) can add more repeating DNA units to the telomere, and consequently elongate it, and keep it dividing as happens in fetal cells, germ cells, stem cells and cancer cells. The challenge of telomerase reactivation is the re-enactment of programmed cellular youth without the autonomy of indiscriminate cancer cellular proliferation.

ACUTE KIDNEY INJURY IS (VERY) BAD NEWS

A rise in serum creatinine following CABG portends bad news: it is the single most powerful risk factor for death post-surgery (Glenn Chertow et, *Am J Medicine*, 1998), predicts extended hospitalization and cost (Glenn Chertow et al, *J American Soc Nephrol*, 2005), and now, in a VAMC cohort published by Areef Ishani et al, Arch Intern Med, 2011, there is a graded (dose of kidney dysfunction) worsening of outcomes following post-CABG acute renal failure leading to established CKD, severity of CKD grade and long-term mortality. The cause of AKI following surgery is not well-defined, but candidates include: renal ischemia/hypoperfusion, low "effective" blood volume, nephrotoxic exposure, pre-morbid CKD, inflammatory cascade triggered by cardio-pulmonary bypass, duration of surgery, systemic microemboli (of debris, tissue, gas and fragment particles) and type of surgical procedure.

IT'S (MOSTLY) ALL ABOUT COMPLIANCE

Resistant hypertension is a common finding in general medicine: an estimated 25% of hypertensives on treatment are poorly controlled. The reasons include inappropriate diagnosis (episodic hypertension), poorly-designed drug treatment, inadequate drug dose, therapeutic non-adherence, secondary hypertension, white-coat hypertension, illicit drug use and true "resistant hypertension". A recent research paper by Bunker et al, *J Human Hypertension*, 2010, suggests that two-thirds of "resistant" hypertension is attributable to poor medication adherence.

the
SECOND OPINION

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FROM THE EDITOR

Medical prognostication, the art of prophesy at the bedside, is fast becoming a dying art. Few true aficionados remain, and I still fondly remember my old Cardiology professor, way back during medical residency, holding the hands of soon-to-be-bereaved family and gently breaking the news of impending death. A quiet gentleman of cultured distinction, with gray beard and diminutive frame, he was never harried, either in his steady pace or measured cadence. An excellent listener, he was all things to those desolate in grief: doctor, friend, shaman and father-confessor. More importantly, he felt your pain, always seemed to know when it was time, and always made the right call. He just knew.

Perhaps, the fault lies in our training, with its current emphasis on science, guidelines and procedures, rather than the finer skills of touch and verb; maybe, it is the unconscionable workload we bear as practicing physicians, affixed sullenly on our brows as a veritable badge of honor; or possibly, another sad reflection on our lack of empathy, symptomatic of an overall coarsening of our culture. There are, of course, other plausible reasons: the conflicting emotions of physicians, conscripted as reluctant eye-witnesses to the solitary experience of dying; the unbid recall of therapeutic lapses and missed opportunities that might have delayed, if not averted certain death; the stress of confrontation with family and loved ones, who might, understandably, be less than partial to the views of the messenger. It is no accident that physicians are heavily invested in the paraphernalia of certitude, the last vestiges of Delphian healing, where god was physician was priest. Nothing shatters that immaculate construct as effectively as the prediction of death, itself a tacit admission of therapeutic, if not personal, failure.

Physicians inhabit a miserable world of death and dying, which we try to engage with science, routine, protocols and superstition: an eclectic mix that allows us to feign optimism, even in the most difficult of times. But illness is brutal and death does not discriminate, therefore that shield of emotional distance is often pierced by empathy and a common humanity. When we are forcefully reminded of our own mortality, our last refuge is the default posture of professional blandness. It is that void that precludes skilled prognostication.

But that which we disdain has been embraced by the chattering classes, the punditocracy of the cable networks, as was given full vent through this winter of Arab discontent. As crowds swept into the streets of Cairo, the usually articulate Tony Blair, special UN envoy to the Middle East and pretty much everywhere else, was on multiple channels offering the usual platitudes, valiantly deflecting attention to the Muslim Brotherhood (a quasi-political organization long neutered by the vengeful Mubarak) and prophesying a future he surely could not see from London. Others made dark allusions to genies-in-bottles, hijacked revolutions, Iran and the economic importance of the Suez Canal- a refrain strongly reminiscent of Margaret Thatcher's millenial pathos over Iraq. Where was Jonathan Aitken, MP, who had then scolded his prime minister for not just being simple minded on the Middle East, but empty-headed- adding, largely for theatrical effect- that said prime minister probably thought Sinai was the plural of sinus?

In this issue of Second Opinion, we offer published guidelines to help doctors with their prognostication skills. In the spirit of this season of Middle Eastern anomie, we also remind our readers of the myth of Cassandra: the patron saint of failed seers and political pundits, who foresaw the Fall of Troy and presumably, her own grisly end, ravaged by Ajax the Lesser and his hordes. As punishment for a forgotten act of human hubris, Apollo had decreed that nobody would ever believe her prophesies, effectively consigning her to a world of perceived clarity and denied certainty. As Le Vay was said to have instructed his surgical staff: "Clarity and certainty are essential to all surgeons in training, at least until they discover that clarity is not enough, and certainty does not exist". And so it was with poor Cassandra; and so it is with our punditocracy. As always, I'll see you Friday lunch-time, at the CME lounge.

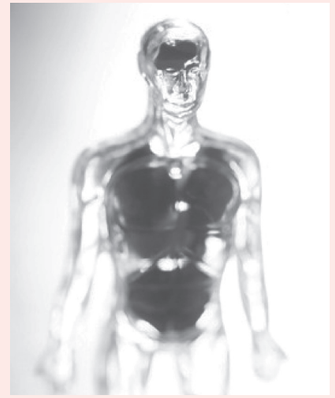
Beze Adogu, MD, Ph.D, FACP

POST-OPERATIVE ATRIAL FIBRILLATION: WHO IS THE FAIREST OF THEM ALL?

Post-operative atrial fibrillation is common, especially after cardiac surgery, resulting in excess post-operative morbidity. The incidence within 4 weeks of major cardiac surgery is estimated at 8-20%. Cardio-selective beta-blockers are often preferred as #1 choice in prevention, in large part because of their tolerability. A head-to-head comparison of bisoprolol (Zebeta) and carvedilol (Coreg) in this situation shows that bisoprolol is superior in preventing atrial fibrillation (Marazzi et al, *American J Cardiol*, 2011).

SHOULD WE MONITOR PLATELET VOLUME IN CORONARY SYNDROMES?

An interesting article by Goncalves et al, *American J Cardiol*, 2011, assesses the value of mean platelet volume as a long-term prognostic marker in acute coronary syndromes. As is well recognized, platelet volume is an indirect indicator of platelet reactivity. Pre-catheterization mean platelet volume was shown to have comparable prognostic power to serum troponin levels in predicting adverse outcomes.



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A BRAND NEW TUMOR MARKER

The history of tumor markers has been dogged by promise and clinical frustration. These biological proteins are typically employed in screening "at risk" populations for cancer; monitoring treatment and recurrence following treatment; diagnosis of specific cancers, and for prognostication in certain cancerous states. The reality is that no bio-marker is fully sensitive or specific. Generally, the more cancer-specific antigens are useful for monitoring but not for diagnosis, such as CEA, Ca 125 and Ca 19-9. On the other hand, the more tissue-specific antigens are of more use in diagnosis, such as thyroglobulin, PSA, beta-HCG and alpha feto-protein.

Renal cancer is a "silent" disease; by the time of diagnosis, it has already metastasized in over a third of patients, and is known to be resistant to chemotherapy. Consequently, 5 year survival for metastatic disease is under 5%. To enable early diagnosis of such tumors, a robust screening assay is needed: Morrissey et al, *Mayo Clin Proc*, 2010 report that 2 proteins (aquaporin-1 and adipophilin) expressed by renal cell cancers and excreted in the urine, might fit the bill. In an accompanying editorial, Grebe & Erickson, *Mayo Clin Proc*, 2010, remind us of past disappointments in this field.

THE FUTURE OF SICKLE CELL DISEASE

Sickle cell anemia is the classic inherited genetic defect: a switch in the DNA code allows the substitution of a single amino acid at the sixth position of the beta-globin chain. This simple chemical substitution results in hemoglobin linking, erythrocyte deformity and intravascular sickling with dire consequences to the patient. Current treatment is focused on preventing sickling, either by prompt treatment of infections (the most common triggers for acute "crisis"), blood cell transfusions (designed to dilute out or otherwise substitute hemoglobin S with normal hemoglobin A), hydroxyurea (which reverses the fetal-to-adult hemoglobin switch from beta-globin to gamma-globin synthesis, therefore hemoglobin F is increased from ~1% up to 20%), and allogenic stem cell transplantation from HLA-matched donors. In the future, treatment for sickl;e cell disease would involve globin gene transfection with (viral) vectors (Cavazzana-Calvo et al, *Nature*, 2010), adult somatic cell reprogramming into pluripotential stem cells (Hanna et al, *Science*, 2007), and interference with the developmental switch in beta-gamma globin gene expression using DNA methylation inhibitors or histone deacetylase inhibitors (Sankaran et al, *Nature*, 2009).

CARDIO-RENAL SYNDROME

Both cardiac and kidney disease have become more prevalent as a result of an aging population, diet and lifestyle changes, and ironically, as a tribute to ICU excellence: patients that would have died some 2 decades ago, are now discharged home with residual kidney/cardiac dysfunction. The high incidence of cardiac dysfunction noted in mild-moderate CKD cannot fully be explained by the "traditional" Framingham risk factors; other underlying factors include L ventricular hypertrophy, anemia, calcium x phosphate product, oxidative stress, endothelial dysfunction, inflammatory index (as captured by CRP profiles) and drug use (including NSAIDs). Also, recent data suggests that the majority of heart failure patients have lowered GFR consistent with grade II or higher CKD. As simultaneous, concurrent and complicating cardiac and kidney dysfunction is common amongst hospitalized patients, it is important to exclude uremic/ischemic cardiomyopathy as well as ischemic/vascular kidney failure before reaching a diagnosis of cardio-renal syndrome. The pathophysiologic mechanisms of cardio-renal syndrome are varied, but each sub-type represents a distortion of the fragile homeostatic response to volume deficit. Five (5) sub-types of cardio-renal syndrome are recognized:

Type 1- Acute Cardio-Renal Syndrome: worsening kidney function secondary to acute heart failure, simulating pre-renal azotemia despite being volume overloaded.
Type 2- Chronic Cardio-Renal Syndrome: poor renal function associated with poor cardiac function, which tenuous equilibrium may be worsened by over-diuresis, persistent hypotension, exposure to nephrotoxic agents, worsening anemia, renin-angiotensin-aldosterone axis blockade.
Type 3- Acute Reno-Cardiac Syndrome: acute cardiac dysfunction as a result of acute renal failure, often as a result of SIRS, uremic syndrome, volume overload, hypertensive crisis, hyperkalemia and other electrolyte disturbances and metabolic acidosis.
Type 4- Chronic Reno-Cardiac Syndrome: chronic kidney disease leading inexorably to cardiac decline, often as a result of diastolic dysfunction, LV hypertrophy, calcific atherosclerosis, volume overload and anemia.
Type 5- Secondary Cardio-Renal Syndrome: systemic illness resulting in concurrent kidney and heart dysfunction, typically from MODS as occurs in sepsis, but also from disorders such as amyloidosis, vasculitis and cytotoxic therapy.

MANAGING MENOPAUSE

If you live long enough, menopause (as well as its associated symptoms) is guaranteed. Menopause is the consequence of pre-programmed ovarian follicular loss. Hormone replacement therapy treats most symptoms of menopause but at a relatively high risk of (cardiovascular) adversity. Consequently, non-hormonal remedies might be used in controlling some common menopausal symptoms. Vasomotor symptoms (such as hot flashes and night sweats) can be controlled by smoking cessation, alcohol limitation, yoga and appropriate relaxation techniques, clonidine, Neurontin, venlafaxine (Effexor) and paroxetine (Paxil). Osteoporosis is best challenged with calcium-vitamin D supplements, biphosphonates, calcitonin, teriparatide (Forteo) and raloxifene (Evista). Vaginal atrophy responds best to topical estrogens, but may respond to vaginal lubricants/moisturizers and regular sexual effort.

THE SCIENCE OF MULTI-VITAMIN SUPPLEMENTS IN THE OVER-NOURISHED

MVI supplementation is a central facet of nutritional therapy in "at risk" individuals, who suffer from or are prone to vitamin deficiency, due to medical illness, anorexia, malabsorption, increased utilization (in infancy, during growth spurts, lactation and pregnancy) and food faddism. Current data does not support MVI supplementation in the healthy American population. Indeed, the health benefits of an improved diet (increased fiber and more vegetables/fruits, decreased refined carbohydrates, saturated fats and salt) are superior to chemical dietary supplementation (Caballero, *Cleveland Clin J Med*, 2010). Additionally, MVI supplements are associated with both dose-related adversity, specific toxicity, and inferior health outcomes in various settings. There were over 58,000 reported MVI-related drug overdoses in 2007 from the National Poison Data System, leading to 17 major adverse outcomes and 1 fatality. Vitamin A toxicity includes intracranial hypertension, increased bone resorption/osteoporosis, desquamative dermatitis and bone pain/premature epiphyseal closure. Vitamin D excess is associated with hypercalcemia, calcinosis cutis, arterial hypertension, short QT interval (and arrhythmogenesis) and nephrocalcinosis. Vitamin E increases bleeding risk (by increasing PT/PTT and inhibiting platelet aggregation) as well as the population risk for all-cause mortality (Miller et al, *Annals Intern Med*, 2005), prostate cancer (Lippman et al, *JAMA* 2009) and hemorrhagic stroke. Vitamin K can induce hemolytic anemia. Vitamin B excess may be related to systemic vasodilation, sensory neuritis and hepatotoxicity. Vitamin C can provoke kidney stones and hemolysis in the susceptible (especially those with G6PD deficiency).

WHEN TO ORDER CT SCANS FOR HEADACHES

Headaches are common, intra-cranial pathology is uncommon. 1% of all ED visits are for headaches (~1 million patients q year) but only 1-4% have an intracranial emergency. The true role of CT is to identify a treatable intracranial lesion (not to avoid a law suit!). Most headaches are just headaches, but it never pays to miss an intracranial lesion. To avoid wasteful use of CT imaging as well as uncovering of "incidentalomas" that have no bearing on the clinical issue at hand, it is worth reviewing indications for CT evaluation in headaches.

1. Thunderclap or Cluster headaches or Atypical headaches (not easily classified into major diagnostic categories of headache).
2. Progressive or New-onset (in those >55 y.o.) of headache
3. Pregnancy-associated new-onset headache
4. Worsening of headache with exertion, Valsalva or stooping
5. History of seizures
6. Signs indicative of systemic disease (fever, rash, palpable purpura) or immuno-compromise (HIV infection or solid organ transplantation) or underlying cancer or local infection (sinusitis, mastoiditis, orbital cellulitis)
7. Abnormal neurologic examination (especially focal neurologic deficits or meningeal inflammation)
8. Visual changes or atypical aura
9. Projectile vomiting or Cushing's reaction (high blood pressure and/or bradycardia)

USING FERRITIN TO ASSESS IRON STATUS

Iron repletion is important in fostering erythropoiesis. However, iron therapy is not without risk, including oxidative DNA damage in blood cells (Kuo et al, *J American Soc Nephrology*, 2008) but probably not an increased infection risk as previously assumed. Serum ferritin is an age-old bio-marker for iron status. Unfortunately, several processes limit its sensitivity as well as specificity as a reliable index of iron storage. Serum ferritin is grossly elevated in inflammatory conditions, malnutrition and neoplastic conditions (Kalantar-Zadeh et al, *Nephrol Dial Transplant*, 2004). Measurements of ferritin are notoriously lab-dependent, with a 15% disparity between laboratories based on methodology and immunoassay of choice. Ferritin levels are hugely influenced by age, sex, diet, medications and genotype. Further, there are wide temporal variations in serum ferritin levels, taken from the same person at different times, by up to 62% depending on time of day and season of year (Ford et al, *Kidney International*, 2008). Different guidelines have published varying "cut off" points for serum ferritin as index for iron repletion: yet, the DRIVE study clearly shows improved hemoglobin responses to IV iron, even with a serum ferritin level up to 2696 pmol/L (Coyne et al, *J American Soc Nephrol*, 2007). Iron status should be evaluated using a combination of ferritin level, transferrin iron saturation and reticulocyte hemoglobin content (Tarng D-C, *Nature Clin Practice Nephrol*, 2009).

PAIN MANAGEMENT IN ORGAN FAILURE

Organ dysfunction is common, as is the need for pain control. The astute physician must clearly understand the risks and projected benefits of his intended treatment, especially as 20% or more of the adult population would suffer significant organ dysfunction at any 1 time. Analgesics can independently trigger organ dysfunction (acetaminophen remains the most common etiology of fulminant liver failure, through the action of its hepatotoxic metabolite, *N-acetyl-p-benzoquinone imine*, in the setting of glutathione depletion) or continued use in organ dysfunction may worsen organ pathology, leading to acute-on-chronic organ failure or death. The pharmacokinetics of analgesic drugs will depend on gastrointestinal mucosal absorption, cardiac output/blood flow, transport mechanics & protein binding, biotransformation in the liver (through drug oxidation, reduction, hydrolysis or conjugation reactions) and biliary/renal elimination. Consequently, cardiac, liver and renal function are the most important considerations in analgesic dosing. Acetaminophen and all NSAIDs are primarily excreted by the kidneys, except Celocoxib which is primarily fecal (57%) and Meloxicam which is primarily biliary (>60%), with some of the rest showing substantial "secondary" elimination routes which might assume primacy of excretion in renal failure: Sulindac/Indomethacin/Etodolac (fecal), Ketoprofen/Diclofenac (biliary). Opiates are typically oxidized or conjugated in the liver prior to renal excretion; therefore, drug clearance is reduced in liver disease, causing undue sedation and/or hepatic encephalopathy, whilst meperidine generates neurotoxic metabolites that can accumulate in kidney failure. As fentanyl and hydromorphone have short half-lives, do not have toxic intermediates, and are least affected by kidney disease, therefore are probably safest to use in either liver or kidney disease. Tramadol is anti-cholinergic, a partial serotonin reuptake inhibitor and can reduce seizure threshold, therefore beware of constipation/gastric atony, serotonin syndrome and epilepsy in recipients.

DEPARTMENT OF NEW DRUGS

1. Anacetrapib, an experimental cholesteryl ester transfer protein (CETP) inhibitor, was able to increase HDL cholesterol levels by 140% and reduce LDL cholesterol by 40% in the DEFINE trial, without noted CVS or electrolyte adversity (Cannon et al, *N Engl J Med*, 2010). This new drug potentially represents the future of lipid management.
2. Afrezza, inhaled insulin in technosphere micro-particle delivery system, is under FDA review as add-on meal-time insulin treatment for type 2 diabetes mellitus. Following the untimely demise of inhaled Exubera insulin (primarily because of its low public acceptance) in 2008, this new edition of inhaled insulin will be watched even more carefully.
3. Odanacatib, a cathepsin K inhibitor, thought to retard osteoclast activity, is under FDA review as a once-weekly oral treatment for post-menopausal osteoporosis. The role of this new agent in what is fast becoming a crowded field remains uncertain, but might prove superior to competing monoclonal antibodies which target osteoclast activity through the RANKL ligand.

WHO SHOULD BE DNR?

Anecdotal evidence to the contrary, in-hospital CPR is often futile. Originally designed to save life following acutely reversible cardio-respiratory arrest resulting from electrical causes or environmental insult (near-drowning, hypothermia, drug overdose), CPR has become "standard of care" for most hospital in-patients. Though 30-50% can expect to survive the initial arrest, only a small minority survive to hospital discharge. Indeed, a Canadian study of in-hospital CPRs (Brindley et al, CMAJ, 2002) show that 22% survive to discharge amongst witnessed arrests (typically in the ICU) whilst 1% survive unwitnessed arrests to discharge (typically on the general floor). Worse, the ability of doctors to predict who would survive CPRs is no better than random chance (Ebell et al, *J Gen Intern Medicine*, 1996). To provide some objective estimates, the Pre-Arrest Morbidity Index (PAM) was developed (George et al, *Am J Medicine*, 1989) allotting 3 points each for pre-identified morbidity factors such as systolic hypotension <90 mmHg, renal failure (creatinine >2.5 mg/dL), homebound status, and presence of underlying cancer, pneumonia or sepsis. None of those with a score >7 survived to hospital discharge.

GETTING IT RIGHT WITH NARCOTIC USE TERMINOLOGY

Proper narcotic management is complicated by a confused description of drug-associated syndromes. The American Society of Addiction Medicine has helped by formulating clear distinctions between the common drug-associated syndromes. *Drug Dependence* describes an adaptative state which manifests a drug withdrawal syndrome triggered by abrupt cessation of drug ingestion, rapid reduction of drug dose, decreased serum levels of agonist drug or administration of a drug antagonist. *Drug Tolerance* is another state of adaptation where drug exposure induces physiologic effects which ultimately diminish the (desirable and/or undesirable) pharmacological effects of the drug over time, at varying rates for each specific effect. *Drug Addiction* is a chronic neurobiologic disease with genetic, psychosocial, behavioral and environmental correlates that influence its full development and clinical manifestation, and is characterized by impaired control over drug use and/or compulsive drug use and/or continued drug use despite evidence of harm and/or cravings for drug. *Pseudo-addiction* describes a focused behavioral pattern designed to obtain drugs in patients with unrelieved pain, but extinguishes on resolution or treatment of painful condition.

FASCINOMA OF THE MONTH: NUTCRACKER SYNDROME

The term "Nutcracker Syndrome" coined by de Schepper in his 1972 paper, describes extrinsic compression of the L renal vein which is entrapped between the aorta and superior mesenteric artery, resulting in L flank pain, hematuria, dilated vascular collaterals (of gonadal, peri-renal and peri-ureteral veins), orthostatic proteinuria, lower limb varicose veins and pelvic vascular congestion (manifest as pelvic pain, dyspareunia, dysmenorrhea, dysuria and vulvar varices/varicocele). In most cases, the aorto-mesenteric angle is <35 degrees, whilst this angle is >45 degrees in controls. Though often found incidentally on abdominal CT images, the diagnosis is clinical, with other components of the syndrome must be delineated. The patient is often a young adult female of asthenic built, multiparous, with chronic left-sided flank pain. It is important to quickly exclude endometrioses and/or nephrolithiases. A screening test with Doppler abdominal ultrasound is helpful if it confirms that L renal vein diameter at the aorto-mesenteric segment/hilar segment has a ratio >4.16 with a peak velocity ratio >3.98 at same segments. Radiologic confirmation relies on MR venography or CT angiography. Treatment entails "watchful expectancy" in less symptomatic cases, stent placement using endovascular techniques, and rarely, vascular transposition of the superior mesenteric artery caudad to the L renal vein.

NEW DRUG TO REVERSE KIDNEY FAILURE?

Phase II trials funded by Reata Pharmaceuticals, Inc, indicate that antioxidant inflammatory modulators (AIMs), using bardoxolone as prototype, could reliably improve GFR when administered over extended periods (at least 6 months) to CKD patients. Improvement in GFR was at least 10% higher than prior pre-treatment baseline, and appeared to be most robust in those with severe CKD. AIMs activate Nrf2, which is a "master gene" or transcription factor, controlling the cellular synthesis of >250 anti-oxidant and detoxification proteins. Therefore, AIMs can block chronic inflammation induced by pro-inflammatory molecules generated by reactive oxygen species, as occurs in chronic hyperglycemia. The data was presented by Pablo Pergola, MD, PhD, at the recent ASN meeting.

WHEN TO REFER TO NEPHROLOGY

I am often asked when is the best time to refer a CKD patient to a specialist: generally, the earlier the better. However, there are many CKD patients (11% of the adult US population) and only so many nephrologists. Referral should therefore be tailored to achieve the most good, in this instance aimed at the reversal or arrest or deceleration of further renal progression. The following indices should guide appropriate referral:

1. All patients with advanced CKD, especially if GFR <30 ml/min
2. Patients experiencing dramatic or progressive worsening in kidney function >15% decline in GFR over 6-12 months
3. CKD associated with multi-system disease such as vasculitis, amyloidosis, myelomatosis, et cetera
4. CKD complicated by uncontrolled/malignant hypertension, bone disease, refractory edema or persistent acidosis/hyperkalemia
5. Suspected renovascular disease, manifest as either renal size asymmetry (>1.5 cm on renal imaging) or abrupt decrease in GFR (by more than 15% following ACE inhibitor/ARB treatment) or non-cardiogenic pulmonary edema (in absence of acute lung injury)