Athens Kidney Center
1440 North Chase Street
Athens, GA 30601

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HEMOGLOBIN A1C IN DIABETES MANAGEMENT

Hemoglobin A1c is a robust and reliable measure of long-term glycemic level, and can be used to monitor glycemic control in diabetics, and also for actual diagnosis of diabetes (without need for obtaining a "fasting" blood sample) provided a clinical laboratory equipment is used, and not a "point-of-care" instrument. Hemoglobin A1c may be lower than expected for chronic level of glycemia in conditions associated with shortened RBC survival (hemolysis, acute blood loss and hemoglobinopathies). Hemoglobin A1c may be higher than expected for chronic level of glycemia in Blacks (Selvin et al, *N England J Medicine, 2010*), the elderly, and in conditions associated with increased RBC longevity (such as post-splenectomy), as well as iron deficiency anemia, opiate addiction, chronic alcoholism, chronic liver disease/jaundice, hypertriglyceridemia, long-term ASA use and lead poisoning. In CKD, hemoglobin A1c levels might be spuriously elevated or decreased, as a result of carbamylation of hemoglobin i.e. a condensation reaction involving the cyanate anion derived from urea) at the N-terminal amino groups, which is "misread" as glycation of hemoglobin in certain assays, or alternatively, an increased RBC fragility in the uremic milieu may lead to lower levels of glycation adducts in CKD erythrocytes.

ALLOPURINOL: NEW KID OR JUST ANOTHER BLOCK?

The xanthine oxidase inhibitor, allopurinol, is of proven effectiveness in the treatment of hyperuricemia and gout, and now comes data suggesting that highdoses of allopurinol could improve exercise tolerance in chronic stable angina (CAD) by Awsan Noman et al, *Lancet 2010*. The mechanism(s) for this observed effect is unclear, though suggested pathways include reduction of oxidative stress (and its effects) within the vascular endothelium, uncoupling of work-energy consumption in myocardium, and possibly, coronary vasodilatation. If these findings are validated in clinical situations, allopurinol could join anti-anginal drugs (such as nitrates, beta-blockers, non-dihydropyridine calcium channel antagonists, and the K-channel activator, nicorandil), statins, ASA, anti-platelet drugs, and renin-angiotensin-aldosterone antagonists as standard treatment for CAD.

ENVIRONMENTAL TRIGGERS ARE GENETICALLY PREDISPOSED

Classic pathogenetic theory requires a genetic "predisposition" and an environmental "trigger", the genetic "soil" being maximal in so-called single-gene diseases such as sickle cell hemoglobinopathy, and the environmental "seed" predominating in common infections such as the common cold. Human immunologic defence against common infections is mediated in part by interleukin-2 signaling, which is itself controlled by the CISH protein (cytokine inducible SRC homology 2 domain protein). A case-control analysis by Chiea Khor et al, *N England J Medicine, 2010*, using over 8000 samples, reveal that genetic variation in the CISH protein greatly influences the response of IL-2 (a cytokine which helps govern T-cell response following an infectious exposure) to common infections, from tuberculosis to acute bacteremia, even to falciparum malaria. In other words, genes control predisposition to infection. How come no one appears too surprised?

ACUTE KIDNEY INJURY FOLLOWING EXERCISE OR SEIZURES

A recent report by M-T Yan et al, Kidney International, 2010, highlights the problem of kidney failure provoked by exercise. This complication also occurs following repetitive seizures, and may be more common during hot summer months. A thorough history followed by appropriate confirmatory tests are the steps to proper diagnosis.

1. Rhabdomyolysis: classically occurs with crush injury or following severe, unaccustomed exercise, but look for pigmenturia (i.e. positive dipstick hematuria without actual identification of erythrocytes in urine specimen), CK should be grossly elevated (often in '000s), and if exercise was relatively trivial, you should search for predisposing myopathic factors such as muscle dystrophy, endocrinopathy (particularly thyroid disease, hypophosphatemia, diabetic crisis, hypokalemia), myositis from viremia, bacterial infections, autoimmune disease/vasculitis), alcoholism, toxins/envenomation or drug abuse (list is extensive, including all alcohols, opiates, cocaine, LSD, NMDA/ecstasy, PCP, amphetamines, hypolipidemic agents, anticholinergic drugs/antihistamines, caffeine/theophylline, SSRIs/tricyclic antidepressants, anti-psychotics, steroids, protease inhibitors and amphotericin B).
2. Hypovolemia: this may be aggravated by NSAID use, ACE inhibitors/ARBs, concurrent diuretic treatment, high humidity, high ambient temperatures, high altitude and atherosclerosis/peripheral artery disease.
3. Metabolic dysfunction: typically from endocrinopathy (thyroid disease, adrenal dysfunction, hypokalemia), glycogen storage diseases, mitochondrial disorders (including MELAS, where the clue may be severe lactic acidemia) and defects in fatty acid oxidation pathway.
4. Sickle cell disease: the clue may be unexplained anemia with signs of marrow expansion, presenting as "bossing" of the skull
5. Hereditary renal hypouricemia: rare disorder characterized by high renal uric acid clearance, resulting in normal uric acid levels despite severe hyperuricosuria, which results in kidney stone disease and kidney failure under anerobic conditions (of exercise).

the SECOND OPINION

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FROM THE EDITOR

Three short stories in quick crescendo: in 1951, a luckless young Negroid lady (remember, this was the 50's), Ms. Henrietta Lacks, was admitted into the segregated medical wards of Johns Hopkins hospital in downtown Baltimore, with an aggressive type of cervical cancer. She was dead within 12 months, but not before her cancerous cells had been harvested without her consent, and later deployed over the coming decades as the prime vehicle for cell biology research (this really was the 50's, remember?). What she lost in longevity- or what Reverend Martin Luther King would refer to as the "grace of old age"- she would gain in scientific immortality as the originating source of HeLa cells. And because it was, well, the 50's, she was condemned to die in penury without health insurance, disability income support or social services. But that minor detail didn't stop a lot of biotechnological companies from reaping a sizable fortune from her singular misfortune.

The ill-fated UGDP trial, published in the Canadian Medical Association Journal, 1976, arrived at several unexpected conclusions. Chief amongst those, was that type 2 diabetics treated with (short-acting) sulfonylurea drugs were prone to unexplained sudden cardiac death. We knew very little then about how sulfonylurea drugs actually worked, and even less about ATP-sensitive K channels, ischemic preconditioning, transmembrane ionic fluxes and the genesis of myocardial irritability. The strident denunciation of that landmark trial- as well as its misbegotten pedigree- assured that its other far-reaching conclusions were swiftly consigned to an inaccessible intellectual ghetto. And that, my friends (to purloin the favorite expression of a political operative), was the first "swift-boat" attack, courtesy of the pharmaceutical industry. The proforma (and anodyne) protestations from the injured authors were efficiently drummed out by the bellicose rebuttal from sulfonylurea manufacturers. To this day, UGDP is seldom brought up in polite conversation.

The intrepid, if somewhat disingenuous group of Sinclair et al, Blood, 2010, reporting on the non-erthrogenic effects of Procrit, flies in the face of conventional wisdom. Now, challenging scientific opinion is neither novel nor unwelcome. But it has to be based on testable facts or hypotheses, otherwise, we risk a repeat of Carl Duesberg (HIV is not the cause of AIDS), Beneviste (water has a memory for serial antibody dilutions), Wakefield (autistic enterocolitis in children)...the list goes on. The ultimate victims are those who will never get cured, because the lines of scientific inquiry were compromised by cant. Just so that you don't miss the connection, Sinclair et al also work for Amgen, a company which you might recall, is basically funded through its subsidized discovery of Procrit. But that, you might say, is entirely beside the point. In a stunning denunciation of the extensive and reproducible science pertaining to erythropoietic stimulating agents, Sinclair et al dismiss any effect of erythropoietin on non-erythrocytic cell lines as either fortuitous, anomalous or laboratory artifact. Interpretation: the pleiotropic effect of erythropoietin as cytoprotectant, anti-inflammatory, vasculotonic, angiogenic and anti-apoptotic autocoid, must be robustly discredited in order to squelch the unseemly rumor that, perhaps, Procrit might have an enhancing effect in tumor growth. Talk about a "scorched earth" policy. To confirm our worst suspicions, a study by Isabelle Boutron et al, in the Journal of the American Medical Association, 2010, highlights the apparently common practice of distorting factual evidence or scientific conclusions in creating titles for trials published in medical journals. The pervasiveness of this practice suggests that "spin" is not restricted to political operatives, embattled British Petroleum executives or hacks employed in the advocacy industry.

Of course, the common link between all these stories is the commercial imperative masquerading as public good. Where should we draw the line? Should big business directly fund scientific research? Should research subsidized by these industries carry a warning of implicit bias? Somewhere, deep south in the Carolinas, Lee Atwater must be laughing in his grave.

As always, I'll see you Friday at the CME lounge.

Beze Adogu, MD, Ph.D, FACP

TREATING H. PYLORI

H. pylori is often likened to a moving target. Management should be based on local susceptibilities and results, and not on consensus algorithms which are often ineffective (Graham & Fischbach, *Gut, 2010*). The classic standardtreatment uses 3 different drugs over 14 days: PPI + clarithromycin + amoxicillin/metronidazole. Best results are obtained from a hybridtreatment protocol (PPI plus amoxicillin x 7 days, then PPI plus amoxicillin plus clarithromycin plus metronidazole x 7 days), with eradication rates >95%; this result is superior to sequentialtreatment with 4 drugs (PPI + amoxicillin x 7 days, PPI + clarithromycin + metronidazole x 7 days) and concomitanttreatment with 4 drugs (PPI + amoxicillin + clarithromycin + metronidazole x 14 days).

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Editor:
Beze Adogu, MD, PhD, FACP

Associate Editors:
Khudr Burjak, MD & Harini Chittineni, MD

Athens Kidney Center
1440 North Chase St • Athens, GA 30601
706-227-2110 (p)
706-227-2116 (f)
www.athenskidneycenter.com

UPDATE ON DIABETES DRUGS

In a meta-analysis presented at the ADA conference last month, Phung et al, report that thiazolidinediones (glitazones), a group of oral hypoglycemic drugs which heighten insulin sensitivity by acting on the gamma subunit of peroxisome proliferator-activated receptors (PPAR-gamma) within the cell nucleus, were indeed superior to all other oral hypoglycemic agents in preventing diabetes. This includes metformin, which has been the drug of choice for this specific purpose, in preventing the transition of pre-diabetes (which afflicts an estimated 60 million of our population) to overt diabetes mellitus. However, not all glitazones are created equal. Another meta-analysis just released by Nissen et al, Archives Internal Medicine, 2010, shows an increased risk of acute myocardial infarction by rosiglitazone, but so far, not by pioglitazone. David Graham et al, *JAMA2010*, report that amongst the elderly using rosiglitazone, there was an increased risk of heart failure, stroke, myocardial infarction and all-cause mortality. Another telling blow following the ORIENT and ROADMAP trials, was on an ARB, olmesartan (Benicar), which is commonly used in hypertensive diabetics. Both trials suggest an unexplained increase in cardiovascular deaths in those patients using Benicar. Added to a recent exposition of increased cancer risk with ARBs (I. Sipahi et al, *Lancet Oncology, 2010*), the FDA is reviewing the risk-benefit analysis for ARBs in current use.

CAD IN ELDERLY WOMEN

A common diagnosis in 40% of elderly women when based on a history of exertional dyspnea (more common symptom of CAD in elderly women, and may present as acute pulmonary edema during an acute coronary syndrome) or angina pectoris (which simulates GERD more commonly in elderly folks), EKG evidence of previous myocardial infarction, positive stress test for myocardial ischemia, characteristic lesions on coronary angiography or clinical findings of acute MI or sudden cardiac death. Risk factors include advanced age, smoking, sedentary lifestyle, history of hypertension/diabetes mellitus, high LDL cholesterol/low HDL cholesterol, presence of LVH, obesity and high serum triglycerides. Acute coronary syndromes in elderly ladies stratify as 50% unstable angina, 35% non-ST wave AMI, 15% STEMI (Woodworth et al, *Am J Cardiol 2002*). Obstructive coronary lesions are best identified by coronary angiography, and myocardial ischemia detected by stress echocardiography. Office treatment following coronary revascularization (if appropriate) should focus on treating modifiable risk factors: BP reduction with ACE inhibitor/ARB or beta-blocker <135/85 mmHg; stop smoking; reduce LDL cholesterol <70 mg/dL; daily exercise regime; structured weight loss; ASA or Plavix as anti-platelet treatment of choice; nitrates for symptomatic relief of angina; avoid hormone replacement therapy; avoid NSAIDs; avoid sulfonyureas (Aronow & Ahn, American J Cardiol2001); avoid excessive diuresis.

IMPROVING DIAGNOSIS OF RENAL CANCER

An incidental renal mass found on routine radio-imaging is a common source of clinical anxiety. Whilst differentiating a solid from a cystic mass mass is relatively easy, solid masses are often subject to more invasive evaluation to exclude cancer. Clear cell cancer of the kidneys account for 85% of kidney malignancies, and is 100% fatal when metastatic. Early surgical nephrectomy is the only viable treatment. New data coming from the REDECT trial demonstrates that a radio-iodine-tagged monoclonal antibody (girentuximab, marketed as Redectane) directed against carbonic anydrase IX (an enzyme preferentially expressed by >95% of clear cell cancer cells) could be used in either a PET or CT evaluation to identify cancer cells, with a positive predictive value of 95%.

FACTITIOUS HYPOGLYCEMIA

Hypoglycemic crisis in diabetics is potentially life-threatening. Frequent recurrence of hypoglycemia demands full re-evaluation of diabetes management. It should be remembered that iatrogenic hypoglycemia from hypoglycemic medications is typically inadvertent, whilst thyrotoxicosis factitia from thyroid supplements is typically premeditated. Clues to factitious hypoglycemia are: ***(a)*** previous psychiatric history or illicit drug use; ***(b)*** medical knowledge, such as nursing or paramedical background; ***(c)*** close family associate (or sibling) of diabetic; ***(d)*** divergent serologic associations (i.e. association of hypoglycemic episode with high plasma immuno-reactive insulin levels, low levels of plasma pro-insulin and/or C-peptide, positive screen for sufonlyurea drug metabolites); ***(e)*** absence of inappropriate insulin use or dosage; ***(f)*** absence of common precipitants of hypoglycemia in previously well-controlled diabetic patient (i.e. chronic kidney failure, liver failure, chronic alcoholism, protein-calorie malnutrition, non-compliance, concurrent hypopituitarism or hypoadrenalism, severe gastroparesis, celiac disease or malabsorbtion syndrome, sepsis); ***(g)*** absence of serologic findings consistent with insulinoma (i.e. elevated plasma insulin levels, elevated C-peptide levels, high insulin/glucose ratio in fasting state, high pro-insulin levels being >20% total immunoreactive insulin content).

FOREVER OF UNKNOWN ORIGIN

Most fevers are innocuous and resolve spontaneously, often within 1 week, before any diagnostic tests are concluded; those are commonly attributed to (viral) infections and are not FUOs. True FUOs are persistent fevers which defy diagnostic or physical localization: those are commonly due to infections(consider visceral abscesses, vertebral/dental abscesses, tuberculosis and culture-negative endocarditis), occult malignancies(particularly in kidneys or liver, as well as non-Hodgkin's lymphomas andmyelodysplastic syndromes), medications(especially antibiotics, NSAIDs, anti-epileptics, anti-histamines, class Ia anti-arrhythmics and anti-thyroid drugs) and connective tissue diseases(especially vasculitis, Still's disease, SLE and polymyalgia rheumatica/GCA) but about half of all FUOs will never be diagnosed (Bleeker-Rovers et al, *Medicine-Baltimore, 2007*). Look for clues such as psychiatric history(factitious fever), skin rash(Still's disease, leptospirosis, secondary syphilis, meningococcemia, disseminated gonococcemia), RUQ tenderness(alcoholic hepatitis), fluctuating blood pressures(high BP suggests phaechromocytoma, low BP suggests Addisonian crisis) and lung symptoms(leptospirosis, psittacosis, Q fever, tularemia and recurrent pulmonary embolism). If no cause is found after extensive evaluation, do not despair: the long-term prognosis is good (Knockaert et al, Archives Intern *Medicine1996*).

CKD IN BLACKS

The most common cause of ESRD in Blacks is diabetic glomerulosclerosis (as in other races), but hypertension is 5x more likely to be causal or associated with CKD in Blacks in comparison to other races. Hypertensive kidney disease is linked to the severity and duration of hypertension, family history of CKD, advanced age, presence of dyslipidemia, smoking status, presence of proteinuria or hyperuricemia, and low socio-economic status. It is unclear if hypertensive CKD is a cause or effect of renal disease, but some data suggest that intrinsic renal dysfunction (possibly, a failure of renal autoregulation of salt homeostasis or a congenitally low nephron number, i.e. oligonephronos) may be the underlying trigger. The AASK trial showed that BP control, irrespective of modality or agent used, was often insufficient to prevent either the development or progression of CKD in "at risk" Black patients. Aggressive BP control <120/80 mmHg may not foster cardiovascular benefits or prevent strokes in CKD patients, but may rather worsen renal outcomes as well as overall survival. The added "renal progression" factor in Black hypertensives appears to be the myosin heavy chain 9 (MYH9) gene, a susceptibility factor that could also explain the high racial preponderance of FSGS, HIV associated nephropathy and post-transplant glomerulopathy amongst Black donor kidneys.Managing Peripheral Artery Disease PAD is common (afflicting 12% adult population in US, climbing to 20% in over-70 y.o. cohort, and 41% of Black women in SHEP study), under-diagnosed (at least 50% are asymptomatic; most common referable symptom being intermittent claudication) and under-treated (treatment often not systematic, and often symptom-directed). Risk factors are advanced age, smoking

history, presence of diabetes mellitus and history of hypertension. Treatment includes smoking cessation, anti-platelet therapy with ASA or Plavix (adding Coumadin was not more effective than anti-platelet drugs alone: WAVE trial, Anand et al, *N England J Medicine 2007*), statin treatment (to reduce LDL cholesterol <70 mg/dL), ACE inhibitor treatment to reduce BP <130/80 mmHg, adequate control of diabetes (which is a proven strategy for microvascular but not macrovascular complications), exercise prescription of 45 mins TIW for at least 12 weeks (shown to reduce symptoms and pain-free walking time: Gardner & Poehlman, *JAMA 1995*), cilostazol 100 mg p.o. BID (which is contraindicated in systolic heart failure), pentoxifylline 400 mg p.o. TID (which has a very modest effect, therefore is typically reserved for situations where cilostazol cannot be safely prescribed) and surgical revascularization (when disease is refractory to medical treatment or there has been development of rest pain/ischemic ulceration or gangrene).

THE VIAGRA MADE ME DO IT

Anupam Jena et al, Annals Intern Medicine, 2010 report that use of drugs for erectile dysfunction in older males was linked to a higher prevalence of STDs, both before actual prescription of the drugs and thereafter. The most common STDs reported were HIV and chlamydiae. This crucial finding suggests that whenever a patient asks for the "blue pill", it is right about time to discuss "safe sex" too.

IS IT TIME TO CHUCK PSA TESTING?

Shao Y-H et al, Archives Internal Medicine2010, present data that patients diagnosed with prostate cancer with a serum PSA under 4 ng/mL typically had low-risk disease but still received aggressive local therapy. In an accompanying editorial comment, Richard Hoffman, MD, lays out the case against routine PSA testing: widespread adoption of PSA as a screening test has resulted in an epidemic of low-risk prostatic cancer, virtually doubling the lifetime risk of prostate cancer diagnosis without any commensurate clinical benefit. Even low-risk disease with a 5 year survival of 100% gets treated aggressively. Cancers that would never cause clinical disease are picked up; note that autopsy reports suggest that 30% of men >50 y.o. harbor microscopic (low grade) prostate cancer at death (from other causes). More damningly, PSA as a screening test lacks both specificity (even at a 4 ng/mL cut-off threshold, many positives are due to BPH or prostatitis) and sensitivity (15% of prostatic cancer have normal PSA levels, and of those, 15% are high-grade cancers despite "normality" of PSA). Therefore, the positive predictive value of a positive PSA for cancer is only 30%. Even worse, PSA did not show any survival benefit as a screen in picking up early cancers in the study by Andriole et al, N England J Medicine2009, a finding supportive of the earlier European study by Coley et al, Annals Intern Medicine1997, that 1400 men screened twice over 9 years was required to prevent 1 cancer death at the cost of diagnosing 48 additional victims. Indeed, the Scandinavian trial published by Bill-Axelson et al, *N Engl J Medicine2005*, shows a survival advantage with prostatectomy as opposed to "watchful waiting" only in patients <65 y.o. At the very least, we probably should not be screening folks older than 75 y.o., and perhaps, not even those older than 65 y.o.; when cancer is found, aggressive care should be dictated by clinical evidence of future cancer progression (such as Gleason score >6, PSA >10 ng/mL, age <55, tumor stage >2a).

ALCOHOLIC LIVER DISEASE

The spectrum of alcoholic liver disease spans fatty liverto foamy degeneration(a rare variant characterized by jaundice and hyperlipidemia) to hepatitisto cirrhosis(characterized by fibrosis and nodular regeneration) and end-stage liver failure(associated with jaundice, encephalopathy and dyscoagulopathy). Diagnosis rests on identifying inappropriate alcohol use (screening protocols include the CAGE questionnaire, which itself depends on the population prevalence of alcohol abuse; its sensitivity is ~70% and specificity is ~90%) supported by clinical/serologic features of alcohol-induced liver damage (physical stigmata of cirrhosis or tender hepatomegaly, concurrent infectionwith hepatitis C in 25-66%, macrocytic anemia, leucocytosis, thrombocytopenia, elevated AST/ALT, elevated gamma-glutamyl transferase, elevated carbohydrate-deficient transferrin [also high in sepsis and anorexia nervosa], elevated ethyl glucoronide [which provides a "delayed" alcohol test, being positive up to 3 days after the last drink], increased hepatic caudate lobe volume with small-sized regenerative nodules on MRI). Typically, elevated transaminases are under 500 IU; higher levels might suggest alternative diagnoses such as viral hepatitis, ischemic/anoxic hepatitis or toxic hepatitis from concurrent Tylenol use. Also, AST/ALT ratio is typically >2, a poorly-explained biochemical artefact which is classically attributed to alcoholics lacking a pyridoxal phosphate cofactor required for ALT activity. The histology of alcoholic liver disease is not diagnostic, and may be similar to biopsy findings in hemochromatosis or non-alcoholic steatohepatitis, though portal triaditis and peri-portal fibrosis appears fairly specific for alcohol-induced liver damage. The "pathognomonic" eosinophilic inclusion bodies of Mallory are present in alcoholic hepatitis, but also in NASH, chronic starvation, jejuno-ileal bypass surgery for obesity, Indian childhood cirrhosis and drug-induced liver toxicities induced by amiodarone or perhexiline. Fatty steatoses of the liver also occurs with alcoholism, but is found in NASH, viral hepatitis (especially HCV infection), Reye's syndrome, fatty liver of pregnancy, mitochondrial disorders, chronic starvation and drug-induced steatosis (from tetracyclines, anti-retroviral agents and valproate treatment). Treatment of alcohol hepatitis starts with abstinence, as all pre-cirrhotic lesions are reversible (including fibrosis but excepting nodular regeneration). On liver biopsy, peri-venular fibrosis and leucocytic infiltration are early markers of disease progression, and should warrant more aggressive treatment. Such treatment may include anti-ulcer gastric prophylaxis, caloric supplements (in presence of encephalopathy, protein restriction has been advocated, or perhaps, use of branched chain amino acids), nutritional support, magnesium supplements, vitamin K/fresh frozen plasma for bleeding (routine use of vitamin K has been controversial, as the problem is not a deficiency, but failure of hepatic utilization of vitamin K in liver disease) and frequent, multiple feeds in part to avoid fasting hypoglycemia. Based on Maddrey's prognostic index in alcoholic hepatitis = 4.6 x [PT - control] + serum bilirubin in mg/dL >32, consider adding steroids or pentoxifylline. Use of biological agents such as anti-TNF monoclonal antibodies, Infliximab, Etanercept have fallen out of favor due to perceived increase in overall mortality in recipients. The use of propylthiouracil (based on finding of peri-central hypoxia similar to that observed following thyroid replacement treatment), colchicine (which has an anti-fibrosis effect), vitamin B6 anti-oxidants (including the vitamin B6-pyrolidone combination marketed as Metadoxine), polyunsaturated lecithins and S-adenosyl methionine (a glutathione precursor) are unproven remedies.

DECONSTRUCTING MALARIA RESISTANCE

The re-emergence of this parasitic infection as a global threat has been associated with the spread of anti-Plasmodial drug resistance, international travel (by natives traveling out of endemic zones, expatriates returning home to temperate/subtropical climates, and pilgrims to the holy sites of the Middle East where the Anopheles mosquito vector exists), and growing resistance of Anopheles mosquito to common insecticides. The result is an estimated 1.1-2.7 million deaths each year, attributed primarily to Plasmodium falciparum. Chloroquine, the drug of choice for treating chloroquine-sensitive disease, binds to a non-protein molecular target, ferriprotoporphrin IX, which is found within lysosomes (food vacuoles) of the parasite. The drug-lysosome complex is toxic to the malarial parasite, resulting in plasmodial cell lysis. Resistance to chloroquine appears to be mediated primarily through gene mutations affecting the Plasmodium falciparum multi-drug resistant gene 1 (mdr 1) or the Plasmodium falciparum chloroquine-resistant transporter gene (crt). Common mutations include the substitution of lysine to threonine at the 76th position in the crt gene (Hayton et al, Curr Drug Targets Infect *Disord 2004*) and aspargine to tyrosine in the 86th position of the mdr 1 gene (Nagasha et al, Trans R Soc Trop Med Hyg2001). New approaches to tackling this global scourge include genetically-engineered mosquitoes incapable of transmitting protozoal parasite; reversal of biological effect consequent upon mdr gene acquisition by parasite (e.g. changes in down-stream transcellular calcium transport); development of safer but effective insecticides; development of non-replicative plasmodial parasite, prevention of hemolysis by reducing erythrocyte membrane porosity of infected cell with poloxamine and other "resins".etc.