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HEART FAILURE BELT IN THE SOUTH-EAST?

We have heard of the Stroke Belt, the Kidney Failure Necklace, The Stone Buckle, and now comes the "Heart Failure Belt" reported by Mujib et al, *American J Cardiol*, 2011. No prizes for guessing where the belt is situated: in the south-eastern United States, covering the states with highest heart failure rates, hospitalization and mortality. You could superimpose 1 on the other: the contiguous states of Alabama (the epicenter, of course), Georgia, Mississippi, Louisiana, Arkansas and Oklahoma. As we do not quite understand this peculiar regional susceptibility to disease, it is hypothesized that low societal awareness, racial susceptibility factors, limited medical access, indifferent medical care, poor resources, marginal clinical coordination and lower literacy levels might all be contributory. How then does one explain the wide disparities between counties within the same state?

DEPARTMENT OF NEW DRUGS: CEFTAROLINE

Ceftaroline is a new, broad-spectrum cephalosporine active against MRSA, multidrug-resistant pneumococci and common gram-negative respiratory and urinary pathogens. It is at least equivalent to Vancomycin plus Aztreonam combination in treating soft tissue and skin infections, and equivalent or superior to Rocephin in treating community-acquired pneumonia. Ceftaroline is administered as fosamil conjugate (pro-drug) IV, at a dose of 600 mg IV q 12 hours infused over 60 mins, and achieves rapid peak plasma concentrations with minimal (less than 15%) protein binding, and first-order elimination kinetics showing primary excretion in urine. As with typical cephalosporins, it has no activity against Pseudomonas or Enterococci, and its activity against Bacteroides is limited (though effective against other anaerobes). Unlike other anti-MRSA agents such as vancomycin (Vancocin), daptomycin (Cubicin), tigecycline (Tygacil), telavancin (Vibativ) and linezolid (Zyvox), this new agent is relatively affordable, with few interactions of note, and generally well-tolerated (though with a propensity for minor GI symptoms such as nausea). Note that only vancomycin and daptomycin are bactericidal, the rest being bacteriostatic; a rising tide of relative resistance threatens the efficacy of vancomycin, as shown by steadily rising MIC levels; and daptomycin is inhibited by lung surfactant, thus rendering it unhelpful for pneumonia treatment.

FAILING NATIONAL GRADES FOR METABOLIC CONTROL

The CDC reports the most recent data culled from NHANES from 2005-2008: 30.9% of American adults are hypertensive, 54.2% of those on treatment are uncontrolled (under 140/90 mmHg) and 30.1% are not receiving any treatment for hypertension. The untreated were disproportionately lacking in regular health access, health insurance or were aged <40 y.o. Those treated for hypertension but remained uncontrolled were disproportionately <40 y.o. or Hispanic. Interestingly, control of hypertension did not depend on insurance status; rates were similar for those with Medicare vs. private insurance, and 90% of the uncontrolled hypertensives actually had insurance coverage. Even worse, 33.5% of Americans are dyslipidemic based on elevated serum LDL-cholesterol, 67% of those being treated are under control, and 52% are not being treated for this serious CVS risk factor (*Morbidity Mortality Weekly Reports*, 2011)! Verdict: improved, but still failing marks.

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a common, eminently treatable, but often undiagnosed clinical syndrome. It is thought to afflict 3-7% of the adult population, though most cases are subclinical. Diagnosis rests on the description of an irresistible urge to move the lower limbs, which is especially worse with inactivity or rest, or late in the evening. There may be associated distal paresthesias, a vague sense of "heaviness", or muscle cramps. Several comorbid illnesses are associated with RLS, but are not necessarily pathogenetic; those include insomnia (being the most common complaint), type 2 diabetes mellitus, clinical depression, chronic renal insufficiency or iron deficiency. There are 2 types of RLS: a primary "idiopathic" type, which is thought to be an autosomal dominant trait and often starts at middle age, progressively worsening over the years. Its underlying pathologic defect is thought to impaired iron transfer within the substantia nigra, leading to impairment of dopaminergic transmission. Secondary "acquired" RLS occurs at any age, and may be caused by pregnancy (in which case, treatment is typically limited to iron repletion), medications (especially dopamine antagonists, neuroleptic agents, anti-depressants and a few anti-hypertensives) or underlying diseases (such as peripheral neuropathy, CVA or end-stage renal failure). Diagnosis is strictly clinical; there are no tests to confirm this diagnosis. Treatment is empirical: sleep hygeine; restriction of stimulants (especially caffeine, alcohol and tobacco); stop all dopamine-depleting drugs; encourage low grade exercise (be aware that strenuous exercise can exacerbate symptoms of RLS); explore idiosyncracies (some patients may respond favorably to compression stockings worn at night, warm showers before bedtime, cold swims before sleep, dietary manipulations, et cetera); choose 1 of 5 drug groups depending on the major presenting symptoms (drug of choice is typically a *dopamine agonist* such as Ropirinole or Pramipexole, but L-dopa and bromocriptine are useful adjuncts despite the risk of "augmentation" with those shorter-acting agents; *anti-convulsant drugs*, such as gabapentin, pregabalin or topiramate, are useful alternative agents in those with disabling neuropathic features; *opiates* such as codeine or hydrocodone can be used to stifle severe pain, but Ultram is notorious for "augmentation" effects; *hypnotic-sedatives* such as zolpidem or temazepam may be employed to help re-initiate restorative sleep; *iron* may be given orally or parenterally in those with proven iron deficits).

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SECOND OPINION

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FROM THE EDITOR

Once more, the soft science of medical guidelines is in the news. Not for any new insights, mark you, but from the public dissemination of age-old practices which are clearly detrimental to its continued survival as a useful force in clinical medicine. Medical guidelines, which were first developed in the early 80s, were never meant as legal stricture or as substitute for lucid clinical thinking. They were generalizable approaches to the management of specific clinical problems, providing an adaptable but formulaic approach to clinical conundrums. Despite its huge potential, guidelines remain a substantially inferior substitute for clinical experience and in-depth knowledge. Regrettably, medical guidelines have since assumed surrogacy for considered clinical insight, providing cover- if not ammunition- for insurance benchmarks, hospital privileges committees, governmental accountability departments, and more sporadically, as laconic exhibits in the litigation trenches of medical malpractice.

When medical guidelines are robust, clinically relevant, free of bias and commercial deference, and fully reflective of current scientific insight and clinical experience, I can think of no better bedside aide to the busy clinician. If those recommendations also show universal applicability, internal consistency, ease of adaptation, reproducibility and cost-effectiveness, credibility is all but assured, even within the ranks of traditional skeptics. For those reasons, several professional medical societies have assumed the task of generating lucid guidelines to support appropriate clinical management. Alas, that awesome responsibility- and the astounding gains to be reaped from subverting it- has not been lost on the pharmaceutical and biotechnology industry.

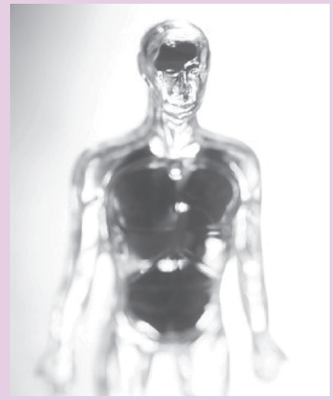
A lot of the recent commentary on guidelines has focused on their derivation (expert opinion vs. placebo-controlled randomized trials), pedigree (individual vs. societal commission), style (simplified vs. heavily referenced) and accessibility (internal consumption vs. public dissemination). Others have used the spreading concern about guidelines to indict other perceived flaws in academic medicine: failure of faculty to disclose outside income and ties to industry; industry-funded subsidy of CME activities and clinical research; suppression of research deemed adversarial to economic interests.... the list goes on. Those considerations, though of some peripheral importance, actually miss the larger point.

In my opinion, the gravamen against guidelines relates to the perception of inherent bias, implicit in the relationship between industry and professional medical societies. For too long, a cosy *menage-a-trois* has existed between organized medicine, pharmaceutical industry and faculty. You might recall the outrage that greeted the National Kidney Foundation's K-DOQI guidelines on bone management in 2004, which was reprised with the release of her 2006 guidelines on anemia management. Then as now, chairmen as well as reviewers within the various committees were either consultants, paid speakers, employees or stock holders in companies with clear financial interests in those guidelines, including Amgen and Ortho Biotech. The insouciant air of *gemutlichkeit* within K-DOQI was soon punctured, first by a blistering jeremiad from the usually soft-spoken Marcia Angell, quickly followed by a phalanx of leading academic nephrologists, such as Jerome Kassirer and Daniel Coyne. Then as now, the standard response was that committee membership, much like the American Express credit card, has its rewards. Sadly, the price for those pecuniary rewards was personal as well as institutional erosion of credibility. To this day, no nephrologist I know of can look K-DOQI straight in the eye.

Yet, guidelines are important adjuncts in medical education, and it is crucial we do not throw the baby away with the dirty bath-water. Faculty, like everyone else, are entitled to a decent living, and whilst letting in sunlight, as provided in Louis Brandeis' famous legal dictum, can act as a potent disinfectant, its effects are prophylactic not curative. We certainly need more transparency, but we also need clear and realistic rules of engagement. Those who accept to lead or write medical guidelines should have no direct industry relations. In return, they ought to be well compensated by the various professional societies, either in cash or in kind, by way of peer recognition. Contrary to the spirit of Marcus Antonius' burial oration for Julius Caesar, we do not ask to bury guidelines, only to reform them.

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

Beze Adogu, MD, Ph.D, FACP



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P WAVE DURATION PREDICTS FUTURE ATRIAL FIBRILLATION

Amongst community-dwelling elderly folk in the Framingham Heart Study, Magnani et al, *American J Cardiol*, 2011, report that the upper 5% of P wave duration was associated with long-term development of atrial fibrillation, even after adjusting for identified risk factors for atrial fibrillation. Now folks, you won't say you weren't warned it was likely to happen.

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CEREBRAL ATROPHY SECONDARY TO ANTI-PSYCHOTIC DRUG TREATMENT

Brain volume is a tricky subject: we do not quite understand what it means, but instinctively suppose it has to reflect brain function. Ho B-C et al, *Arch Gen Psychiatry*, 2011 report on a 7 year neuro-imaging study on schizophrenic subjects that chronic anti-psychotic drug use leads to irreversible cerebral atrophy. The intensity as well as duration of anti-psychotic drug use were both related to the degree of brain atrophy. Recall that schizophrenia itself also induces brain atrophy, regardless of treatment. Indeed, the brains of schizophrenics have very low "grey matter" substance, showing an average 6% volume loss in the amygdala, hippocampus and parahippocampus- the areas critical for memory storage and information retrieval. Also, mental maturation in adolescence is associated with brain volume loss, presumably due to "pruning" of superfluous synaptic pathways. Finally, the brain of substance abusers tend to be smaller than average, though if that represents cause or effect of drug misuse remains controversial.

HOW LOW IS LOW?

From the ACCORD trial, we now recognize that high blood sugars mostly risk microvascular (and macrovascular) attrition, but low blood sugars risk death. From ON TARGET, we learnt that low systolic (or diastolic) blood pressures were associated with higher mortality in a J-type relationship. Chrysant & Chrysant, *American J Cardiol*, 2011 flesh out the details of a J-curve in hypertension management: below a diastolic BP of 70-80 mmHg or systolic BP below 130 mmHg, incidence of acute MIs increase 3x or more in those with coronary artery disease (especially if not revascularized) or LV hypertrophy; the cerebral circulation, which unlike the coronary circulation depends mostly on systolic not diastolic BP, is better auto-regulated over a wider range of BP profiles and is therefore not subject to a J-curve response; low BP levels predispose to acute cardiac syndromes but not to acute strokes.

IRON IS NOT HARMFUL IN INFECTIONS. SERIOUSLY.

Since Murray, Murray, Murray & Murray, *British Med J*, 1978 published an article suggesting that iron-deficient Somalian nomads were more likely to suffer from infections (malaria, brucellosis and tuberculosis) following oral iron repletion, generations of medical students have been raised with an irrational fear of iron repletion. Chronic anemia is common during infections, typically as anemia of chronic (inflammation) disease, a complex disorder with impaired iron metabolism, shortened RBC survival, erythropoietin resistance, and relative as well as absolute erythropoietin deficiency. Few (mostly gram-negative) microbes are iron-dependent for growth, such as E.coli, Klebsiella, Salmonella, H. influenza, Pseudomonas, Yersinia and Listeria, but there is no evidence for increased infection rates with iron repletion, and with the exception of Vibrio infections, none of these infections are more common in hemochromatosis subjects (Jurado, *Clin Infect Dis*, 1997). Data from critical illness (Pieracci et al, *Surg Infect*, 2009) and ESRD patients (Brewster et al, *Nephrology*, 2005) on iron therapy do not show an increase in infection rates. Maybe, it is time to let go of this myth.

ICU UPDATE: IATROGENIC LACTIC ACIDOSIS

Lactic acidosis is common in the ICU setting: diagnosis relies on clinical suspicion and serologic testing (perhaps, aided by quick demonstration of an unexplained anion-gap metabolic acidosis- recall the mnemonic AT MUDPILES from last month's edition). Type A ("primary") lactic acidosis is triggered by systemic hypoperfusion in shock-like states. Type B ("secondary") lactic acidosis follows liver/renal failure, metastatic cancer, alcoholism or medications (that interfere with peripheral tissue perfusion or subvert pyruvate-glycolysis metabolic pathways or cause mitochondrial cytopathy). The common iatrogenic (medication-related) causes are: biguanide hypoglycemic drugs (Metformin), nucleoside reverse transcriptase inhibitors (zidovudine, stavudine, didanosine and lamivudine), tetracycline, propofol, linezolid, beta-adrenergic agonists, epinephrine/norepinephrine and isoniazid. Rarely, lactate may accumulate from propylene glycol metabolism which is often used as a diluent for NTG, phenytoin and etomidate.

INDIRECT (NON-BIOPSY) DIAGNOSIS OF LIVER CIRRHOSIS

Cirrhotics may present *in extremis* thereby precluding safe liver biopsy. Indirect serologic and imaging tests may help arrive at the true diagnosis, based on demonstrating advanced fibrosis which is characteristic of cirrhosis: (1) ultrasonographic demonstration of liver atrophy (typically asymmetric, with pronounced R lobe atrophy with paradoxical L lobe/caudate lobe hypertrophy), nodularity of hepatic surface and increased echogenicity; (2) ultrasound or magnetic resonance elastography (based on transmission of low amplitude/low frequency waves which travel with maximal velocity through dense or fibrotic tissue); (3) evidence of portal hypertension or hypersplenism, often manifest as pancytopenia (with normal/hyperactive bone marrow response), peritoneal ascites, encephalopathy; (4) presence of fibrosis-related serum markers (especially high titers of procollagen type 3 amino-terminal peptide, a.k.a. P3NP); (5) reversal of ALT>AST dominance (ratio reverses from >1 to <1).

HEART ATTACKS IN THE AGE OF RECESSION

Duke university researchers (Fiuzat et al, *American J Cardiol*, 2010) tracked rates of acute MIs from 2006 to 2009, relating those to stock market scores on NASDAQ, as a surrogate for public perception of economic well-being. After adjusting for seasonal changes in heart attack rates, there was still a close relationship between periods of stock market decline and spikes in heart attack rates. Maybe, there is something after all in those urban legends of "fat cat" Wall Street types keeling over whilst watching the DJIA ticker-tape of economic extinction in late 2008.

STRESS DOSE STEROIDS IN TRAUMA

Hydrocortisone use is expanding in the ICU setting: the rationale is that systemic inflammatory response syndrome predicts nosocomial infection (Bochicchio et al, *J Trauma*, 2001), and underlying ICU-related disease is a risk factor for secondary adrenal insufficiency, so-called critical illness-related corticosteroid insufficiency (Annane et al, *JAMA*, 2008). The long-awaited HYPOLYTE study examined the role of continuous IV hydrocortisone (starting at 200 mg/day x 5 days, and tapering over the next 2 days) in multiple trauma victims (Roquilly et al, *JAMA*, 2011). Those on IV hydrocortisone were statistically less likely to suffer nosocomial pneumonia or hyponatremia. What sets this study apart from previous trauma studies (e.g. CRASH trial) is pre-treatment short corticotropin test, culling out only those patients with signs of critical illness-related corticosteroid insufficiency.

CRANBERRY OR NOT?

It started as an old wife's tale, then grew into an urban legend, and was later stamped by the magisterial elan of the *New England Journal of Medicine* when Howell et al, reported in 1998, that polyphenolic extracts from cranberry juice (so-called proanthocyanidins) were able to inhibit the adherence of P-fimbriated E. coli to the bladder mucosa. Now comes a rebuttal from Barbosa-Cesnik et al, *Clin Infect Diseases*, 2011, showing that a "real world" randomized placebo-controlled trial of cranberry juice vs. other vitamin-C rich juices in college students failed to demonstrate any protection by the fabled cranberry juice. Case closed? Not on your nelly. It turns out that vitamin C in the placebo might contribute an independent bacteriostatic effect (based in part, on its higher relative acidity) as well as the possibility that these college students were better hydrated during the trial (a.k.a. the "placebo effect") resulting in only 14% recurrence rate for UTIs amongst the placebo cohort (in real life, you'd expect a 25-36% recurrence for a "null" effect). Those on cranberry juice had an expected 20% recurrence rate (therefore, the problem was not so much with the cranberry juice, but the gang-buster placebo). Perhaps, vitamin-enriched "placebos" are not merely placebos in UTI trials.

SUN EXPOSURE, VITAMIN D AND MULTIPLE SCLEROSIS

Ever wondered why multiple sclerosis is more common the further away you go from the equator? Lucas et al, *Neurology*, 2011, report that high levels of sun exposure and (higher) vitamin D levels were independently associated with a significantly lower risk of central demyelination in MS: the risk of a first demyelinating event (FDE) dropped by 30% for each 1000 kJ of UV radiation, as did the highest quintiles of serum vitamin D levels with a 7% drop in demyelinating events for each 10 nnmol/L rise in vitamin D levels. Perhaps, I should also point out that solar/actinic keratoses, autoimmune disorders, diarrheal illness, cystic fibrosis, clinical depression, societal affluence, longevity and liberal democratic politics also trend higher the further you move from the equator.

DIALYSIS PATIENTS WITH CORONARY ARTERY DISEASE

Nephrologists seldom agree with their cardiologists as to the optimal treatment for ESRD patients in need of cardiac intervention: finally, Herzog et al, *Circulation*, 2010 (abstract #12633) sheds some light on this conundrum using the USRDS data-base. In ESRD patients requiring cardiac revascularization, drug-eluting stenting is the best short-term strategy, having better overall survival rates up to 12 months post-intervention. However, from 18 months on, those with CABG as intervention-of-choice had better survival rates. This was largely because of a high peri-procedural mortality of 8.5% amongst ESRD patients undergoing CABG; thereafter, there is a steady loss of life from steady CVS attrition, with a cross-over of relative mortality between 12 to 18 months, favoring CABG recipients long-term. Maximal benefit was observed in CABG patients who received an internal mammary artery as conduit of choice. Predictors of poor outcome following cardiac intervention were: age >75 years, non-Black ancestry, presence of congestive heart failure, and use of peritoneal dialysis as modality of choice.

HEART ATTACKS TRIGGERED BY SEXUAL ACTIVITY

Dahabreh & Paulus, *JAMA* 2011, perform a timely meta-analysis of papers linking episodic (sexual) physical activity and acute coronary syndromes. Episodic physical exertion increased the risk of an acute MI by 3.5x and sudden cardiac death by 5-fold. The risk was higher in the sedentary or otherwise inactive, and if the specific physical trigger was repeated 1x each week, the risk of cardiac misadventure dropped by 30-45%, more for acute MIs and less for sudden cardiac deaths. Moral: regular physical exertion is good for you; if it is only going to occur on Valentine's Day, don't bother.

MISSED DIAGNOSIS: RENAL PAPILLARY NECROSIS

Renal papillary necrosis is not uncommon in hospital practice, though the diagnosis is often missed. The presence of necrotic slough in the urine should immediately suggest the diagnosis. Common causes of papillary necrosis can be remembered using the mnemonic *POSTCARDS from LA*: pyelonephritis, obstruction/obstructive uropathy, sickle cell disease, tuberculosis (of kidneys), cirrhosis (of liver), analgesic abuse, renal vein thrombosis, diabetic nephropathy, systemic vasculitis/shock, lithiases (stone disease) and alcohol abuse.

FINE-TUNING THE PREDICTIVE ALGORITHM FOR CARDIAC DEATH

Every resident knows the 5 predictors of impending cardiac death: low systolic blood pressure (usually <110 mmHg), high levels of beta-natriuretic peptide (usually >550 pg/mL), high BUN levels (usually >50 mg/dL), elevated pulmonary capillary wedge pressure (typically >21 mmHg) and low levels of peak oxygen consumption (typically <14 ml/kg/min, during cardio-pulmonary exercise testing). Researchers from UCLA report that BNP and peak oxygen consumption were the strongest predictors for death or emergency cardiac transplantation amongst 1,215 patients referred to their hospital with advanced heart failure (Sachdeva et al, *American J Cardiol*, 2010).

FEVER FOLLOWING TRANSFUSIONS

Not all fevers associated with transfusions are hemolytic, allergic or infectious; but those remain are 3 major worries in the febrile blood recipient. An acute rise in ambient blood temperatures (by more than 1.5 degrees F) within 36 hours of a transfusion should indicate: (1) Acute Hemolytic Reaction in 1 per 10,000 transfusions (immediate destruction of infused RBCs by recipient complement-fixing antibodies directed against ABO-surface antigens intravascularly typically against ABO blood group antigens); (2) Delayed Hemolytic Reaction in 1 per 1000 transfusions (after 1 week post-transfusion following extravascular RBC destruction within the liver/spleen of anti-Rhesus immunoglobulin-coated erythrocytes; it is important to exclude extravascular hemolysis from concurrent hypotonic fluid administration or mechanical trauma within narrow-guage needles or tubing); (3) Allergic in 1 per 50 transfusions (often non-febrile, and more commonly associated with skin manifestations or pruritus, but could also be anaphylactoid with bronchospastic, hypotensive or gastro-intestinal symptoms); (4) Infections in 1 per 250,000 transfusions (have become less common with universal adoption of screening protocols, and HBV transmission occurs in 1 of 350,000 transfusions, HCV in 1 of 1.8 million transfusions, HTLV in 1 of 2 million transfusions, HIV in 1 of 2.3 million transfusions in America; it is important to exclude bacterial transmission from contaminated bags/blood (chiefly by bacteria which can survive low temperatures, such as staphylococci, Yersinia and Citrobacter), drug-related fevers concurrent with transfusion, parasitoses (chiefly malaria and trypanosomiasis in cosmopolitan centers) and sepsis syndrome; (5) Non-Hemolytic Non-Infectious Transfusion Reactions in 1 per 50 transfusions (secondary to repeated antigenic exposure from prior transfusions or pregnancy, resulting in antibody-mediated release of cytokines such as IL-1, IL-6 and IL-8, being more common following platelet transfusions than RBC transfusions, and partially prevented by leukoreduction of RBCs).

DO WE UNDERSTAND HOW THE PPD TEST WORKS?

Health organizations everywhere ask for a PPD test (by which they really mean a Tuberculin Skin Test, a.k.a. Mantoux test) from their staff. It's only when the results are "positive", that clinical confusion sets in: What do we do next? The Mantoux test is the skin response to type 4 (delayed hypersensitivity reaction, based on the Coombs & Gell classification) response to a standardized dose of tuberculin purified protein derivative (0.1 mL of 5 tuberculin units). A positive test is a measured diameter of skin induration (not erythema) of >10 mm at the test site (some health groups advocate using 5 mm based on the local epidemiological risk for tuberculosis exposure) after 48-72 hours of antigen challenge. A positive test proves cell-mediated immunity to tuberculin antigens, which in turn infers exposure to mycobacterial antigens at least 2-10 weeks prior to skin testing. Positivity therefore means latent tuberculosis (most likely), active tuberculosis (unlikely in the absence of other clinical features of infection), infection with non-tuberculosis mycobacteria (e.g. mycobacterium ulcerans) and BCG vaccination (usually the response from previous BCG vaccine wanes over the years). The Mantoux test is often negative in the immuno-compromised (dysfunctional cell-mediated immunity) as well as in septic patients, undernourished, elderly, post-vaccination (with live viruses), lymphocytic disorders, ESRD and during "active" clinical infections from any source (including, paradoxically, tuberculosis). Summary: a positive Mantoux is potentially serious and, based on risk of recent TB exposure, should be treated (most active TB cases occur within 2 years of initial exposure); a negative Mantoux test should only be interpreted only within its clinical setting, and may require repeat testing after 4 weeks (Booster Effect).