Athens Kidney Center
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LESSONS FROM THE EMERGENCY ROOM

Confusion and other lapses in cognitive status are common in the alcoholic. A recent case in the Emergency Room reminded me- yet again -of the myriad complications of chronic alcoholism, and how easily those could be missed, or dismissed as "just being drunk".

1. Alcohol intoxication: should be supported by signs of current inebriation, an alcohol fetor, elevated blood alcohol levels and a history of recently normal/lucid behavior prior to acute drinking binge.
2. Seizures and post-ictal state: supported by focal jactitations and/or abnormal EEG tracings with epileptiform wave discharge. In the alcoholic, seizures may be triggered by alcohol itself, an organic brain syndrome resulting from chronic alcohol use, " alcohol withdrawal syndrome" or brain injury, classically due to a subdural hematoma.
3. Sepsis syndrome, often with hypotension but not necessarily with fever; consider aspiration pneumonitis, Klebsiella bacteremia, bacterial peritonitis, ascending cholangitis and disseminated tuberculosis.
4. Withdrawal syndromes and delirium tremens: especially if there are signs of motor and autonomic overactivity (including fever, diaphoresis, palpitations and hypertensive urgency) and visual hallucinations.
5. Hypoxemia from any cause, including pneumonia or heart failure.
6. Psychiatric morbidity, including (undiagnosed) dementia, clinical depression, et cetera.
7. Medication-related: the list is endless, but beware especially of sedative-hypnotics, anti-convulsants, neuroleptic agents/anti-psychotics, quinolone antibiotics, steroids, digoxin, et cetera.
8. Head trauma which may result in subdural hematoma or intracranial bleeding elsewhere; be particularly mindful of this in patients concurrently treated with anticoagulants or anti-platelet drugs.
9. Metabolic syndromes, including hypercalcemia, hypomagnesemia, hypoglycemia (often occurring after 6 hours but not later than 48 hours of latest binge- which helps distinguish this clinically from DT, which often occurs after 48 hours of latest binge), lactic acidosis, ketoacidosis, et cetera.
10. Hepatic encephalopathy.
11. Nutritional encephalopathies, including the thiamine-responsive Wernicke-Korsakoff syndrome.
12. Rarities: cerebellar hemorrhage/degeneration, central pontine myelinolysis (following introduction of hypertonic solutions, either 3% saline or lactulose), demyelination of corpus callosum (Marchiafava-Bignami disease)

MANAGEMENT OF RESTLESS LEGS SYNDROME

1. Non-Drug Treatment: sleep hygiene/regular sleep-wake cycle, adequate rest, low-grade exercise in day-time, reduction in emotional stress.
2. Withdrawal of Provoking Medications: alcohol, nicotine, caffeine, beta-blockers, neuroleptics/anti-psychotics, anti-depressants (both tricyclics & SSRIs), lithium.
3. Management Of Associated Disorders: (a) early delivery in pregnancy; (b) treatment of peripheral sensory neuropathy; (c) treatment of kidney disease; (d) treatment of rheumatoid arthritis and/or other vasculitic disorders; (e) treatment of Sjogren's/sicca syndrome; (f) treatment of monoclonal gammopathy of undetermined significance; (g) correction of iron deficiency with oral iron supplements; (h) correction of folic acid/vitamin B12 deficiency; (i) correction of magnesium deficiency
4. Drug Treatment:

(a) Non-Ergot Dopamine Agonists: pramipexole (Mirapex) 0.125-0.5 mg p.o. QHS, ropinirole (Requip) 0.25-5 mg p.o. QHS; drugs in this group may cause nausea, dizziness, orthostatic hypotension, sudden sleep attacks and impulsivity. Bromocriptine/parlodel is even less tolerable, and levodopa/carbidopa is more likely to trigger augmentation/rebound effects making either drug less useful for this indication.

(b) Iron Supplements: Iron Sulfate 325 mg p.o. BID-TID between meals (best with vitamin C 250 mg p.o.), if there is evidence of iron deficiency; risk of gastrotoxicity is high

(c) Slow-Release Gabapentin/Horizant 300-600 mg p.o. QHS, which is FDA-approved for RLS, in contrast to the off-label (and probably ineffective) use of clonazepam and other benzodiazepines as well as codeine and other opiates.

the SECOND OPINION

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FROM THE EDITOR

There are 2 kinds of doctors: those who love eponyms, and those who do not. I love medical eponyms; I'd hate to see them disappear. There are probably as many eponyms as there are diseases, ranging from Addison's disease (of adrenal insufficiency) to Zieve's syndrome (of alcoholic liver disease) and so many half-forgotten names in-between. Many are restricted by geography, politics, history, convention- and even grammar- to isolated users. Medical students would be shocked to learn that Plummer-Vinson syndrome in Boston is the same entity as Patterson-Kelley syndrome in London. The Bostonians were first in 1912, and once again, fair England loses. What we know as POEMS is called Crow-Fukase syndrome in Japan.

Some eponyms are suitably shrouded in controversy: witness the drive to delist Wegener's disease, named after Friedrich Wegener, a gifted pathologist, but alas, also a committed member of the Nazi Party whose rapid ascent in academia was probably facilitated by human experimentation. He wasn't the only one: Hans Reiter- of Reiter's syndrome- was similarly afflicted, and his eponymous syndrome is now known as reactive arthritis, a particularly insipid substitute. Ditto for Dr. Julius Hallevorden. Which begs the question: why do the best minds often fall prey to demagogues?

For me, eponyms are the spice of medical literature, adding zest and zing to many forlorn illnesses, and providing a serial commentary on the nuances of medical culture. It's improbable but true that there are Kerley A, B and C lines, and would you believe it, Billroth I coexists peacefully with Billroth II in an anatomic distinction as tenuous as that between louse and flea. Some eponyms seemed designed only to inflict distress: whose auscultatory prowess was ever improved by knowing the derivation of Austin Flint, Carey Coombs or Graham Steell murmurs? In innocent times before HIPPAA became law, eponyms were used to shield sensitive health information from inquisitive ears- as was the case with Hansen's disease for leprosy, and sotto voce, the French disease (if you were English, and of course, the English disease if you were Gallic) for gonorrhea. Some names are tricky: Tietz syndrome refers to familial albinism-deafness, whilst Tietze's syndrome is the better-known costochondritis syndrome. There are some over-achievers: Sir James Paget gave his distinguished moniker to diseases of the bone, breast and penis. Talk about a man of diverse interests! Despite what medical residents might think, Fitz-Hugh-Curtis perihepatitis was described by 2 people not 3: Fitz-Hugh is actually 1 man, not two. Graves disease is a perennial stumbling block: Robert Graves described goitrous thyrotoxiciosis, making Graves or Graves' or even Graves's disease acceptable, but never Grave's. In like fashion, Cori disease was published by the duo of Carl and Gerty Cori: therefore, there ought not be an apostrophe after i. In America, maternal expectancy is tempered by the fear of Down syndrome, whilst our European cousins call it Down's. Pedants would insist on distinguishing Basedow disease (another term for Graves disease) from Basedow syndrome (which follows iodine intake), and split hairs over Barlow disease (of scurvy) and Barlow syndrome (of floppy mitral valves): Karl von Basedow described the earlier, John Barlow the latter. But I have seen professors- who ought to know better- tripped by Andersen disease (described by Dorothy Andersen) versus Anderson disease (after William Anderson).

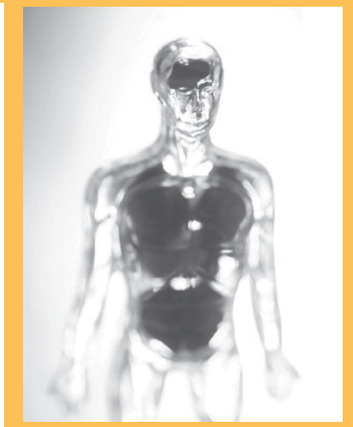
Whilst eponyms may transport us to distant cities, my recollections are laced with misgivings and uncertainty: Lassa- as in the arenavirus hemorrhagic fever- is a desolate area in northern Nigeria; Legionnaires were convening- not holidaying, mark you- in Philadelphia; Lyme is the backwaters of Connecticut; Berlin, not Bornholm, is the place to visit. The fabled Jerusalem syndrome in the spiritually delusional, brings to mind another nasty virus, Ebola, and Calabar swellings, caused by loa loa filariasis along the Bight of Biafra. Most eponyms were actually named after doctors- a puny attempt at self-immortalization you might say- but a few have placed some unfortunate patients at the vortex of medical history: Lou Gehrig's disease was named in honor of the baseball great but acknowledged by common usage only in America; hemophilia B immortalizes the unfortunately-named Stephen Christmas, and of course, there's Hartnup disease, vaguely remembered from pre-Med biochemistry. I'm sure those immortals, all to a man, would have gladly forsaken fame in medical texts for a normal life shorn of guest appearances at medical Grand Rounds.

When words fail, numerals become ready substitutes: first disease refers to measles (a common paramyxovirus exanthem of childhood), creating a precedent for fifth disease (a.k.a. erythema infectiosum from parvovirus B19) and even sixth (roseola infantilis). Some eponyms are really acronyms laced with cryptic clues: who would wish HELLP on their worst enemies, or the deceptively-named CADASIL syndrome, laying waste to both brain and power? Some names appear repetitively, such as Cushing's triad defining the characteristic findings of intracranial hypertension, Cushing's syndrome bespeaking overactive adrenal glands, and Cushing's ulcer of an eroded gastric wall. The eminence of Cushing was matched if not bested by the French neurologist, Jean-Martin Charcot, after whom was named Charcot-Leyden crystals in allergic lung disease, Charcot-Marie-Tooth disease, Charcot's neuropathic joint, and to the everlasting woe of hapless surgical residents, Charcot's triad in bacterial cholangitis. Some eponyms were lifted straight from myth and literature: Charles Dickens gave us the Pickwickian syndrome; Greek mythology gave us hermaphroditism, hebephrenia and narcissism; the Bible was the origin of Job's syndrome, the unjustly afflicted sage of Old Testament lore, whose pestilence is now explained by failure of neutrophil chemotaxis. A few eponyms are hostage to societal convention: you are encouraged to diagnose Brugada syndrome (even though it was described by 2 brothers, and really ought to be Brugadas syndrome), Hakim-Adams syndrome of normal pressure hydrocephalus is somewhat iffy, but calling restless legs by its true name of Ekbom syndrome is widely thought to betray the intellectual show-off. I like the curiosity of Bombay phenotype, a neat biological explanation for most false accusations of bastard birth. Three eponyms even I could do without: chikungunya is an inaccurate description (unlike kwashiokor, which precisely labels the "displaced child" in protein malnutrition), Asherson's (anti-phospholipid antibody syndrome) is somewhat superfluous, and referring to prune belly syndrome as Eagle-Barnett syndrome is a bit like calling AIDS the Montagnier-Gallo disease.

I love eponyms, even in infamy: wouldn't it be a more fitting punishment to retain Wegener's eponym as a public example of the dangers in mixing good science with racial cant? And doesn't the old name sound better - with more gravitas- than the proposed moniker of polyangiitis with granulomatosis?

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

Beze Adogu, MD, Ph.D, FACP



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UNDERSTANDING COCAINE ADDICTION

Recent neuro-behavoioral research has tried to distinguish the biology of cocaine addiction (repetitive or compulsive use) from "incidental" (goal-directed) use: Mize et al, *Proc Natl Acad Sci*, 2011, report that chronic cocaine exposure results in gene alteration in the "reward" circuit of the brain, deep within the nucleus accumbens. Cocaine reduces heterochromatic histone trimethylation, which in turn triggers global destabilization of the neuronal genome, disrupting the tight control of gene transcription in the brain. Cocaine acts as a dopamine agonist, which by blocking dopamine re-uptake transporters within terminal nerve endings results in high dopamine levels in neuronal synapses, the biological basis for the cocaine "high" which experientially mimics the clinical symptoms of paranoid schizophrenia. It is thought that early (non-repetitive) drug use, which is typically voluntary or "goal directed", becomes compulsive over time, in part as a result of "learned" responses, Pavlovian-type conditioned reflexes, and the impact of altered chemistry in dopaminergic centers. Several threads of evidence had implicated opiate neuropeptides such as dynorphin and enkephalins, both in the basal ganglia as well as other parts of the neocortex, as putative reinforcers of cocaine use. Now, we know that long-lasting gene alteration in the brain might also help reinforce the permanency of cocaine addiction.

IN OBESE, GENOTYPE PREDICTS PHENOTYPE POST-SURGERY

Obesity is part genetic and part environmental: the summation of genes, medical comorbidity, diet, lifestyle and caloric excess. Not surprisingly, there is now evidence that genetics predict response to bariatric surgery. Still et al, Obesity, 2011, report from the Geisinger Obesity Research Institute, Danville, PA, that genetic variation within 4 obesity-related genes (FTO, INSIG2, MC4R and PCSK1) predict the ability of patients with severe obesity who underwent Roux-en-Y gastric bypass surgery to keep off the weight. The higher the allelic burden, the greater the risk of post-surgical obesity.

NOT ALL THIAZIDES ARE CREATED EQUAL

Diuretics are indicated for the treatment of hypervolemic states and clinical hypertension. Generally, thiazide diuretics suffice in most conditions except where there is renal dysfunction, mandating use of a loop diuretic. As Messerli & Bangalore, *Am J Medicine*, 2011, remind us, all thiazides are not equal, with significant differences in efficacy, complications and long-term outcomes including morbidity and mortality. When thiazides are indicated, chlorthalidone or indapamide should be used- not hydrochlorothiazide. As 1 of my professors once remarked, "if hydrochlorothiazide was not so easily abbreviated as HCTZ, no one would ever use it".

PREDICTING KIDNEY FAILURE IN SEPSIS

Acute kidney injury is common in the ICU, and septic shock is a typical underlying cause. In an observational cohort study, Plataki et al, *Clin J Am Soc Nephrol*, 2011, reviewed risk factors for renal failure amongst 390 consecutive admissions with septic shock at 1 institution (Mayo Clinic, Rochester) of whom 61% developed kidney failure. The statistics were dismal: there was 34% mortality amongst patients with septic shock but without kidney failure, rising to 49% mortality in those with both septic shock and kidney failure. Development of acute kidney failure was independently associated with (1) delayed introduction of antibiotics for septic shock; (2) transfusion with blood products; (3) presence of an intra-abdominal focus/abscess; (4) use of renin-angiotensin aldosterone system (RAAS) antagonist such as an ACE inhibitor or ARB; (5) high BMI. In this scenario, once again time is kidney: it should be noted that for each 1 hour delay in initiation of appropriate antibiotics, there was a 3% increase in the incidence of renal failure. Also, each 1 kg/m2 increase in BMI was linked to a 2% increase in the incidence of renal failure. Conversely, for each 1 mL/min increase in baseline GFR there was a corresponding 1% fall in the incidence of renal failure. Moral: once sepsis is suspected, start immediate treatment with IV antibiotics based on assumed causal organisms- the lab tests can wait.

NEW DOGS FOR OLD TRICKS: ANTIBIOTIC-INDUCED DIARRHEA

There are no shortage of ideas to treat Clostridium difficile infection: antibiotics (to kill the pathogen), probiotics (to compete against the pathogen) and anti-toxins (to sequestrate the toxin). Yet, the central irony of its management is that this antibiotic-induced infection (such as Clindamycin) is commonly treated only by introducing yet another antibiotic (such as Vancomycin). Savidge et al, *Nature Med*, 2011, report that the gastrointestinal mucosa responds to C difficile infection by s-nitrosylation of its enterotoxin, essentially neutralizing and inactivating the C difficile toxin. It turns out that for C difficile enterotoxin to gain entry into mucosal cells where it causes cellular inflammation and death, it has to be first cleaved into smaller fragments by activated cysteine protease, a process described as a "molecular guillotine". Cysteine protease (the cleavage enzyme) is activated when the enterotoxin binds to a cellular autocoid known as InsP6, whilst the protease is in turn inactivated by the natural defense mechanism of s-nitrosylation. Without cleavage of toxin by cysteine protease, the enterotoxin is denied access into the intestinal mucosal cell, and intestinal disease is aborted. The researchers are now searching for a vehicle to induce s-nitrosylation as the first line of attack when C difficile is diagnosed.

COFFEE FOR DEPRESSION?

A large longitudinal study by Lucas et al, *Arch Intern Med*, 2011, found that caffeine, the ubiquitous methylxanthine psychostimulant most readily consumed as coffee, decreased the risk of clinical depression in women over a 10-year study period. Importantly, the trend appeared to be follow a dose-response curve, and was in support of previous observations linking reduced suicide risk to coffee consumption. However, before we all adopt coffee as anti-depressant of choice, several key questions remain unanswered: Can these findings be extrapolated to males? Is there a threshold level for coffee consumption before these effects are noticeable? Why are other caffeinated beverages - and methylxanthines, such as tea- apparently unable to confer similar psychoprotective benefits? Are the beneficial effects of coffee age-restricted or in some ways age-dependent? Is this relationship causal (cause-effect) or consequential (effect-causation)- in other words, is it that coffee reduces depression or that the depressed shun coffee?

LIFE EXPECTANCY WITH HIV: THE NEW NORMAL IN UGANDA

Despite being treated with older, more toxic and less effective regimen than are being used in most of the Western world, life expectancy amongst HIV-seropositive patients has significantly improved even in resource-poor settings such as Uganda. Mills et al, Ann Intern Med, 2011, in a prospective cohort study report that those who start combination ART treatment at age 20 years can reasonably expect 26.7 additional years of life, whilst those starting treatment at 35 y.o. can expect another 27.9 additional years. In these United States, patients starting ART at age 20 can expect to live another 49 years. However, in Uganda, the average life expectancy at birth for all citizens is 55 years. Predictors of longer survival include female gender (as has also been found in Western countries) and higher CD4 count at onset of treatment.

THE END OF VACCINE DENIAL?

On August 25, the Institute of Medicine released its recent study on vaccine-related adversity, based on over 1000 original papers: www.iom.edu/Reports/2011. In brief, vaccines as with other therapeutic agents/biologicals, are associated with adverse reactions, but those are rare, usually reversibly, and none are linked to either development of type 1 diabetes mellitus or autism. Influenza vaccine may cause transient respiratory tract symptoms but will not trigger or exacerCommon side-effects include faintness, soreness at injection site and low-grade fever. Rare side-effects include anaphylaxis (with MMR, varicella, inactivated influenza, hepatitis B, meningococcal, human papillomavirus and tetanus), febrile seizures/encephalitis (MMR), transient arthralgias in women and children (MMR) and facial edema/conjunctivitis (inactivated influenza). Those with severe immunodeficiency may be susceptible to encephalitis (MMR) and cerebral edema/pneumonitis/hepatitis/meningitis plus clinical varicella/shingles (varicella vaccine).

PREVENTION OF POST-MENOPAUSAL BREAST CANCER

Aromatase inhibitors (Aromasin/exemestane, Femara/letrozole, Arimidex/anastrozole), by blocking aromatase enzyme which converts androgens into estrogen, essentially prevent estrogen synthesis in post-menopausal women. A recent placebo-controlled double-blind trial studied the effect of an aromatase inhibitor (Aromasin) amongst post-menopausal women considered at higher risk for breast cancer development (based on 1 of 4 factors: age >60 y.o., 5-yr Gail score >1.66%, prior precancerous lesion in situ, prior mastectomy with ductal carcinoma in situ). Participants in this study by Goss et al, *N Engl J Med*, 2011, were followed over a mean period of 35 months and showed a significant drop in annual incidence of invasive breast cancer by 65%. Aromasin substantially reduced the risk of invasive cancer (as well as cancer precursor lesions such as atypical ductal/lobular hyperplasia) in this high-risk population without any associated serious drug-related adversity and only with minimal or no change in quality of life. Aromatase inhibitors will likely join anti-estrogens such as Raloxifene/Evista (which may be less effective as an anti-cancer prophylactic) and Tamoxifen (which confers an increased susceptibility to uterine cancer/secondary malignancies and DVT) as possible prophylactic agents for post-menopausal breast cancer in high risk individuals.

VAMPIRE SYNDROME IN CARDIAC PATIENTS

Frequent phlebotomy has long been a concern in hospital medicine: it leads to anemia, results in worse outcomes (including mortality), is often of dubious value (doctors do not always act upon or check the results), and now, based on Salisbury et al, *Arch Intern Med*, 2011, we know just how common this practice is as well as its associated complications. By collating data retrospectively from 57 centers, a database including 17,676 patients with acute MI, Salisbury et al, found that 20% of patients developed new-onset hospital-based anemia (defined as a drop in hemoglobin from normal to <11 g/dL). For each 50 mL of blood drawn, the risk of developing anemia increased by 18%. The average blood draw amongst those who developed anemia was 173.8 mL in contrast to 83.5 mL amongst those who did not develop anemia. Interestingly, there was a 2-fold inter-hospital variability in blood volume removed at phlebotomy, with "large-volume" blood-draw hospitals generally experiencing higher rates of phlebotomy-induced anemia. The authors suggest that using pediatric tubes, limiting routine lab draws, recycling stored serum samples for additional diagnostic testing, and "underfilling" blood tubes could help remedy this new drain on patient (and hospital) resources. A previous study by Thavendiranathan et al, *J Gen Intern Med*, 2004 had shown similar findings on the internal medicine service at Toronto General Hospital: phlebotomy led to mean changes in hemoglobin of 7.9 g/dL during acute hospitalization, with hemoglobin changes dependent on volume of phlebotomy (for each 1 mL of phlebotomy, hemoglobin dropped by 0.07 g/dL), length of hospitalization, age of patient (younger patients had a relatively larger change in hemoglobin with phlebotomy), pre-admission hemoglobin, Charlson comorbidity index, and admission intravascular volume status (volume-depleted patients had a larger change in hemoglobin levels).

TREATING DEPRESSION IN DEMENTIA

Distinguishing depression from dementia is often problematic: several key symptoms are common for both disorders, including social withdrawal, memory lapses, sleep disturbances (sleeping too much or too little), impaired concentration and loss of interest in prior activities. The demented patient is often a taciturn or unreliable historian, and behavioral features attributed to either depression or underlying dementia may reflect other co-morbid medical conditions, including endocrinopathy. Severe depression may masquerade as dementia, the so-called pseudo-dementia of depression. However, a striking decline in mood and/or anhedonia often signals the development of depression in the chronically demented patient. Appropriate treatment is salutary, as dementia is irreversible whilst depression is eminently correctable with proper treatment. A recent randomized, double-blind, placebo-controlled study by Banerjee et al, *Lancet*, 2011, suggests that drug treatment with sertraline or mirtazapine was no better than placebo for depression in dementia and should not be offered as "first-line treatment" in mild-to-moderate depression amongst the demented population. The study did not explore the potential impact of non-pharmacological treatment in depression, which may include the inferred benefit of specialist referral.

AGGRESSIVE CANCER CARE & ENDOWMENT

Racial disparities exist across the full spectrum of health, and not surprisingly, there is now evidence that there are also substantial differences in cultural perception of aggressive cancer treatment. Data from the Cancer Care Outcomes Research & Surveillance study by Martin et al, Cancer, 2011, show that there are underlying ethnic differences in the willingness to expend personal financial resources in extending life. Overall, most minority groups were more likely than Caucasian patients to willingly sacrifice personal resources in extending life during treatment of newly-diagnosed lung/colorectal cancer. Even after correcting for age, quality of life and disease stage/prognosis, African-Americans were 2.4% more likely to willingly exhaust personal financial resources in treatment, though single status, divorce/separation and ignorance about life expectancy were all associated with a greater willingness to use personal funds to extend life. Overall, 80% of African-Americans, 72% of Asians, 69% of Hispanics and 54% of Caucasians reported a willingness to deplete personal funds in order to prolong life.

OPIATE USE IN FIBROMYALGIA: WHERE ARE THE GUIDELINES?

Fitzcharles et al, *Am J Medicine*, 2011 provide a timely overview of opiate use in fibromyalgia. Fibromyalgia has become a common diagnostic label, despite the hazards of verification: it relies on a subjective assessment of symptoms described by patients without external confirmation, objective/laboratory correlates or reliably effective treatment. No current guidelines recommend opiate use in fibromyalgia, yet over 50% of patients are treated with opiate narcotics. The side-effects of opiate misuse including fatigue, sleep disturbance, increased pain from opiate-induced hyperalgesia and dysphoric mood are all common features of untreated fibromyalgia, further complicating the dissection of iatrogenic disease from native fibromyalgia. Furthermore, other medical illnesses including unstable mental disorders, drug-seeking behavior, vasculitis, are commonly mistaken for fibromyalgia: it is time to develop reproducible diagnostic criteria for this disease, identify effective remedies, and stick with those.