

COMMENTS AND RESPONSES

Exercise and Peripheral Arterial Disease

TO THE EDITOR: Dr. McDermott and colleagues (1) found that self-directed walking exercise at least 3 times weekly was associated with a slower rate of functional decline in patients with peripheral arterial disease (PAD) after adjusting for sociodemographic and clinical characteristics, including aspirin, statin, and angiotensin-converting enzyme inhibitor use. They also took into consideration that a proportion of patients benefited from participating in supervised exercise programs. They did not, however, adjust for the use of pharmacologic interventions for claudication, such as pentoxifylline and cilostazol, which might have more significant and direct effects on functional performance than those seen with aspirin, statin, and angiotensin-converting enzyme inhibitor therapy for concurrent cardiovascular risk factor modification. In a recent meta-analysis (2), treatment with pentoxifylline, a methylxanthine derivative, was shown to increase total walking distance on a treadmill by almost 44 meters (95% CI, 14 to 74 meters). Therapy with cilostazol, an inhibitor of phosphodiesterase type 3 with antiplatelet and vasodilator effects, also significantly improved maximal walking distance, quality of life, and functional status in randomized, placebo-controlled trials (3, 4). Therefore, the slower rate of functional decline observed among those who walk for exercise regularly should probably not be attributed to the beneficial effect of self-directed exercise without taking into consideration the use of pentoxifylline or cilostazol therapy.

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Potential Financial Conflicts of Interest: None disclosed.

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TO THE EDITOR: The recent article by McDermott and colleagues (1) serves to strengthen the growing body of evidence for the health benefits of regular walking. The authors showed that walking for physical activity at least 3 days per week is not only feasible for patients known to have reduced quality of life (2) because of PAD but can also be self-directed outside of the supervised clinic. The cost savings of this finding have potentially enormous implications that require further economic analysis.

The attenuation of functional decline among those who indi-

cated a walking frequency of more than 3 days per week is an important finding; however, we feel these data become even more meaningful when combined with the average walking speed of approximately 3.9 km/h (the average of the functional measures of ambulation shown in the authors' Table 1). Those patients who walked less frequently also walked more slowly, making it difficult to separate the effects of frequency from intensity. Walking speeds of less than 4.0 km/h are often defined as less than moderately intense physical activity (<3 metabolic equivalents [METs]) (3); however, the long-term benefit of increased functional capacity that is gained by walking more than 3 times per week at these slower speeds is clinically relevant. Maintaining functional capacity would contribute to sustaining or improving cardiorespiratory fitness, which is a powerful and well-established predictor of cardiovascular disease morbidity and mortality (4).

Defining and translating an understandable and efficacious walking goal are imperatives for clinicians and their patients. Although these authors highlighted the importance of walking frequency, the contribution of walking speed to reducing the decline in functional capacity is also probably important. In a study of a group of people with type 2 diabetes (a risk factor for PAD), we found that "normal" walking speed approximates 3.3 km/h (5). When these participants increased their walking speed to approximately 5.1 km/h (3 times per week for 30 minutes), their resting heart rates significantly improved—suggesting improved cardiorespiratory fitness (unpublished data). For symptom-limited patients (such as those with PAD), we suggest prescribing a walking goal that includes frequency, speed (intensity), and time components. We recommend a walking goal of approximately 5.0 km/h, which equates to a patient-friendly, pedometer-based pace of about 120 steps/min, for 30 minutes (3600 steps) at least 3 days per week.

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We agree with Dr. Kim that cilostazol and pentoxifylline, the only 2 U.S. Food and Drug Administration–approved

Table. Adjusted Associations between Frequency of Self-Directed Walking Exercise and Functional Decline over 3-Year Follow-up in Persons with Peripheral Arterial Disease*

Outcome Measure	Functional Decline by Group (n = 417)			
	No Walking	Walking 1 or 2 Times/Week	Walking ≥3 Times/Week	P Value for Trend
6-minute walk, ft	-79.19	-73.42	-44.40	0.048
Usual-paced 4-meter walk, m/s	-0.048	-0.030	-0.016	0.019
Fastest-paced 4-meter walk, m/s	-0.070	-0.052	-0.025	0.012
Summary performance score	-0.498	-0.451	-0.228	0.130

* Analyses adjusted for age, sex, ethnicity, previous year's functional level, comorbid conditions, leg symptoms, educational level, ankle-brachial index, body mass index, cigarette use, Geriatric Depression Scale score, cilostazol use, pentoxifylline use, and patterns of missing data.

drugs for treating walking impairment in patients with PAD, have modest effects on walking performance in this patient population. Therefore, we repeated the analyses that we reported in our manuscript with additional statistical adjustment for use of pentoxifylline or cilostazol. Our results (Table) did not change substantially from those reported in our manuscript. Therefore, self-directed walking exercise is associated with slower rates of functional decline in persons with PAD, independent of the use of pentoxifylline and cilostazol therapy or other confounders.

We appreciate the comments of Mr. Johnson and Dr. Bell. Unfortunately, we did not measure the intensity of walking exercise of participants in our study and therefore are not able to comment on associations between intensity of walking exercise and functional decline in our cohort. However, Gardner and colleagues (1) demonstrated similar improvement in walking performance in patients with PAD who were randomly assigned to a low-intensity versus a high-intensity exercise walking rehabilitation program.

We found that participants with PAD who walked for exercise more frequently demonstrated less functional decline in the 4-meter walk. Although we did not measure walking speed during exercise, our analyses adjusted for performance during the previous year. Consequently, our findings were independent of walking speed as determined during the previous year's visit. To determine whether our findings were similar among patients with PAD who had different levels of performance, we also repeated our analyses after we stratified participants according to baseline performance. Our results suggested that participants with PAD whose baseline performance was poorest, such as those with slowest walking speed, achieved a benefit from the self-directed exercise program that was similar to or greater than that seen by other participants with PAD.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

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Body Mass Index and Risk for End-Stage Renal Disease

TO THE EDITOR: Hsu and colleagues (1) found a significant correlation between body mass index (BMI) and subsequent renal replacement therapy. Perhaps because of the generous sample size, lengthy follow-up, or survival bias, the relationship was more substantial than previously reported. This finding provides an important insight in determining the significance of BMI in the development of renal disease, a relationship that is both complex and not yet fully understood.

Although increased BMI may be associated with the development of renal disease (and subsequent renal replacement therapy), it is an association that may change throughout disease progression. Studies examining risk factors for progression of renal disease and mortality among patients with established chronic kidney disease (CKD) have found modest or no correlations between outcome and BMI (2, 3). After patients require renal replacement therapy, increased BMI is associated with increased survival (4). This phenomenon has been referred to as “reverse epidemiology” or “the dialysis-risk paradox” (5).

Potential explanations for these seemingly contradictory results include both physiologic and methodologic reasons. Co-occurrence of diabetes and hypertension seems to have a probable effect on the development of kidney disease in obese individuals. In addition, research has established that increased BMI leads to glomerular hyperfiltration, which may independently lead to renal disease (6). After renal disease has been established, the impact of BMI may be obscured by other pathologic processes, including malnutrition, inflammation, and changes in vitamin D metabolism. Finally, the roles of survival bias, reverse causation, and timing of competing risk factors need to be considered when exploring the possible cause of reverse epidemiology. The outcomes reported by Hsu and colleagues and other investigators provide insight into this complex relationship and are likely to play an important role in determining how clinicians manage patients with renal disease.

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TO THE EDITOR: The strong association between obesity and the risk for end-stage renal disease (ESRD) that Hsu and colleagues (1) reported is a valuable addition to the list of risk factors for ESRD. It seems possible, however, that these findings are influenced by survival bias (2), especially if obese individuals with CKD have a paradoxically better survival chance than nonobese individuals. An inverse association between obesity (including morbid obesity) and survival has been frequently shown among patients with advanced CKD who undergo maintenance hemodialysis (3). Therefore, it is possible that even obese patients with earlier-stage CKD (that is, those who do not yet require maintenance dialysis) may have a significantly higher likelihood of surviving and reaching ESRD than nonobese patients with CKD, many of whom may die before progressing to more advanced stages. Keith and colleagues (4) showed that the risk for death among patients with earlier stages of CKD is as much as 10 to 20 times higher than the risk for progression toward ESRD. Because far more patients with CKD die than ever reach ESRD and because obesity might confer survival advantages in CKD, it would seem important to reevaluate these data while considering possible survival biases for obesity.

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Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: We thank Drs. Thorp, Kalantar-Zadeh, and Kopple for their interest in our study, in which we showed that increased baseline BMI is a strong risk factor for ESRD. They questioned whether persons with CKD who are obese have paradoxically better survival than those who are not obese and whether what has been called “reverse epidemiology” could explain our findings.

We would like to emphasize that our study was not limited only to those persons with baseline CKD. Overall, 1036 out of 1471 cases of ESRD developed among individuals who did not have baseline CKD (defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m², or proteinuria or hematuria by dipstick urinalysis). In the overall cohort, as expected, those with increased BMI had a higher risk for death from any cause (Table).

We also point out that increased BMI remained a risk factor for mortality in the subgroup of persons who had baseline CKD (Table). As shown in Table 3 of our paper, increased BMI was a strong risk factor for ESRD among those with and without baseline CKD. Together, these data strongly argue against the presence of important survival bias as an explanation for our findings.

Table. Association between Categories of Body Mass Index and Risk for Death

Category	Relative Risk (95% CI)*	
	Entire Cohort (n = 320 252)†	Persons with Baseline Chronic Kidney Disease (n = 44 583)‡
Normal weight (18.5–24.9 kg/m ²)	1.00	1.00
Overweight (25.0–29.9 kg/m ²)	1.04 (1.02–1.06)	1.03 (0.99–1.07)
Class I obesity (30.0–34.9 kg/m ²)	1.20 (1.17–1.24)	1.19 (1.12–1.27)
Class II obesity (35.0–39.9 kg/m ²)	1.42 (1.35–1.50)	1.32 (1.19–1.47)
Class III obesity (≥40.0 kg/m ²)	1.71 (1.58–1.86)	1.53 (1.30–1.81)

* Adjusted for period of multiphasic study, age, sex, race, educational level, smoking status, history of myocardial infarction, serum cholesterol and creatinine levels, proteinuria, and hematuria.

† Of the entire cohort, 55 425 patients died before the onset of end-stage renal disease.

‡ Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m² (using the Modification of Diet in Renal Disease Study formula) or as the presence of proteinuria or hematuria by dipstick urinalysis. Of this group, 11 768 patients died before the onset of end-stage renal disease.

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Saving (Internal) Medicine

TO THE EDITOR: We should not be surprised by the observation that the exodus from careers in general internal medicine may be more rapid than previously recognized (1, 2), and this should be a warning to those interested in the health and welfare of the United States. To me, a practicing generalist, these observations validate what seems apparent in the day-to-day practice of medicine: Physicians and trainees are speaking with their feet by fleeing generalist careers. Ironically, this is occurring at the very time when our country needs more generalists to coordinate the care of the growing elderly population with complex health care needs.

Such observations as those reported are instrumental to sounding the alert. I would estimate that finding solutions will require a radical redesign of many key features of the medical infrastructure in our country, ranging from medical school training to how and what we reimburse in the delivery of care. Although some might argue that being a generalist is inherently unattractive in our technologically oriented society, I would argue that the exodus from general internal medicine is mostly related to perverse incentives that pervade our system.

I suppose that several stars will probably need to align if we are to find and execute effective solutions. First, cooperation between the specialties and subspecialties of medicine will be necessary for recognizing the value of well-trained generalists and the need to compensate them appropriately. Second, we will need to identify leaders with the courage to take a stand against those vested in maintaining a dysfunctional status quo. Third, the public must recognize that new procedures and expensive technology are not the only things we need in medical care. Finally, articulate thought leaders in medicine need to propose comprehensive solutions, such as the Advanced Medical Home concept and the American College of Physicians' redesign of medical training papers that are under way.

Unfortunately, the demise of general internal medicine looms as a possibility. If that happens, it will be to the considerable detriment of the health and welfare of the nation. We as physicians, individually and through our organizations, need to work together to prevent that from happening.

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Potential Financial Conflicts of Interest: None disclosed.

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2. Sox HC. Leaving (internal) medicine [Editorial]. *Ann Intern Med.* 2006;144:57-8. [PMID: 16389255]

TO THE EDITOR: A thoughtful editorial (1) bemoans a decline in the number of practicing internists but admits to a paucity of information in literature and among physician workplace researchers to explain its causes. I have previously made comments (2) relevant to this problem. Thirty years of practice as an internist allow me to make further observations.

Academic medicine is the carpenter that fashioned the coffin of internal medicine. Instead of reengineering internal medicine to accommodate change, it cannibalized the discipline by reducing its worth, creating the hospitalist and ambulatory care internist. These were both nails that helped seal the coffin; the former reduced the influence of the internist in the acute care environment, and the latter blurred distinctions between internists and those without medical degrees who practice in ambulatory care settings.

Medical subspecialties that are nurtured in the ivory towers of academia have further reduced the stature of the internist. Effective lobbying by their affiliated societies and by commercial manufacturers of the medical devices they use assured them disproportionately higher reimbursement than that of their generalist colleagues. Absent an identity, the internist's only remaining role is thought to be that of provider of ambulatory care to the chronically ill whose medical problems are beyond procedural intervention and lucrative compensation.

A continuing decline in professional stature and income, when coupled with deteriorating working conditions, makes the continued existence of internal medicine untenable. I am pessimistic that current political and professional interests will allow significant change to resuscitate internal medicine. Would it then not be opportune to draft an obituary for internal medicine and commission a requiem to its memory?

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Potential Financial Conflicts of Interest: None disclosed.

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CLINICAL OBSERVATIONS

Laboratory Infection of a Technician by Mimivirus

Background: We recently reported the discovery (1) and genome sequencing (2) of the largest currently identified virus on earth, the mimivirus (Figure). This virus growing in amoeba was mistaken for a bacterium because it stained gram-positive. It was first isolated from a cooling tower in Bradford, United Kingdom, during the investigation of a pneumonia outbreak. We observed a high level of

seroconversion to the mimivirus in patients with pneumonia (3). Because the pathogenicity of the virus is not yet established (4), we do not use specific procedures for its manipulation. A technician from our laboratory in Marseille, France, recently presented with acute pneumonia and mimivirus seroconversion. The technician regularly performed Western blot assays, including ones that documented infection with the mimivirus.

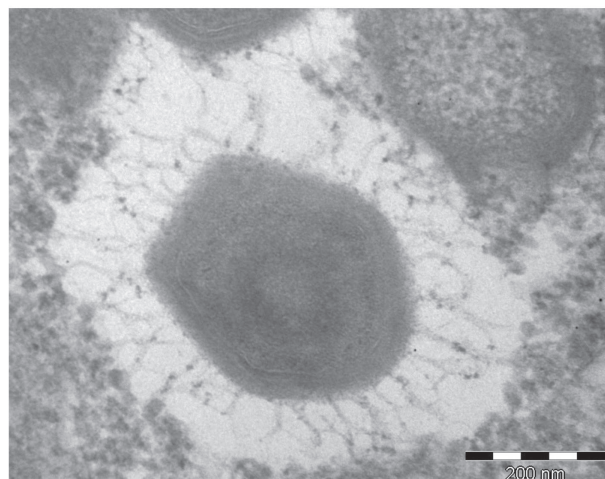
Case Report: The technician was a 38-year-old man who was tested yearly for antibodies against microorganisms that he manipulated in Western blot assays. He had never previously exhibited antibodies to the mimivirus. On 15 December 2004, he experienced a dry cough that had worsened during the night. Approximately 15 days after the onset of the cough, he presented with fever (temperature, 39 °C), chills, weakness, and productive cough. Treatment with amoxicillin–clavulanate, 2 g/d for 8 days, was initiated. On day 23, he returned for follow-up evaluation because his symptoms had not improved. In addition to weakness and productive cough, the patient also reported transfixing pain in his chest. A radiograph of the chest showed bilateral basilar infiltrates suggesting viral pneumonia. Results of serologic studies for usual pneumonia-causing agents were negative, but mimivirus seroconversion from less than 1:50 to 1:3200 was documented (3). The patient slowly recovered.

We used electrophoresis to test the patient's serum. Mimivirus particles were purified as previously reported (2), and soluble proteins were processed for isoelectric focusing analysis on a Multiphor II electrophoresis unit (GE Healthcare, Uppsala, Sweden). Second-dimension separation was then performed on an Ettan DALT unit (GE Healthcare) with 10% polyacrylamide gel at 50 watts per gel for 30 minutes, followed by 17 watts per gel for 4 to 5 hours. Resolved proteins were stained by using a method compatible with mass spectrometry (5), and spots were excised. After in-gel digestion with trypsin solution (Promega Corp., Madison, Wisconsin), the resulting peptides were analyzed with a MALDI-TOF mass spectrometer (Bruker Daltonics, Wissembourg, France). Mimivirus proteins that were resolved by 2-dimensional gel electrophoresis were transferred onto nitrocellulose membranes. The membranes were blocked for 1.5 hours in phosphate-buffered saline containing 0.2% Tween-20 polyoxyethylene-sorbitan monolaurate detergent (Sigma Aldrich, St. Louis, Missouri) and 5% nonfat dried milk. Each membrane was then probed with serum from the patient (1:50). After incubation for 1 hour, the membranes were washed 3 times in phosphate-buffered saline and Tween-20; they were then incubated with goat anti-human secondary antibody that was conjugated with horseradish peroxidase (Southern Biotechnology, Birmingham, Alabama) in a ratio of 1:1000. An ECL enhanced chemiluminescence system (GE Healthcare) was used for detection.

On electrophoresis, the patient's serum sample reacted strongly to mimivirus proteins (23 reactions). With 1 exception, all reactions corresponded to proteins of unknown functions, and 4 were encoded by genes unique to mimivirus. When the membrane was probed with serum that had been collected from the same patient a few months earlier, no reaction was detected.

Discussion and Conclusion: Antibodies to mimivirus were initially detected in a group of Canadian patients with community-acquired pneumonia. In serologic testing in this group, seroconversion to mimivirus was more common than seroconversion to any other tested agent (3). However, the cause of the pneumonia could not be definitively attributed to mimivirus because of the potential

Figure. Mimivirus virion as viewed by transmission electron microscopy.



for unknown cross-reactions that might lead to falsely elevated serologic values.

The case presented here provides additional evidence that the mimivirus may be a cause of clinically important infection. The technician was exposed to the virus, developed pneumonia, and exhibited seroconversion to 23 different specific proteins—4 of which were encoded by very specific genes without homologue in the National Institutes of Health GenBank. Therefore, cross-reactions were unlikely. The inefficacy of antibiotic treatment and the negative results of tests performed on other antigens reinforced our opinion. Serologic seroconversion does not establish causality, however; therefore, further isolation of the mimivirus from an infected patient is now mandatory. However, we believe that the mimivirus should be considered a pneumonia agent and should be treated as a class 2 pathogen.

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Octreotide-Induced Manic Episodes in a Patient with Acromegaly

Background: Psychotic reactions have been well documented in patients receiving therapy with low doses of bromocriptine (1) and other dopaminergic agonists. Dopamine stimulates somatostatin release. In animals, somatostatin influences a wide spectrum of behavioral functions, including learning, regulation of slow-wave sleep, and locomotor activity. These functions are often altered in patients with manic episodes (2), and some alterations have also been described in humans after administration of octreotide (3).

Objective: To describe a patient with acromegaly in whom the administration of the long-acting somatostatin analogue octreotide precipitated a manic episode on 2 occasions.

Case Report: Acromegaly was clinically and biochemically diagnosed in 1990 in a 33-year-old woman. The patient also had diabetes that required insulin therapy 3 times daily. She underwent pituitary surgery and radiation therapy in 1991. Serum levels of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone were decreased after these procedures; treatment with estrogen and L-thyroxine was begun. Because plasma growth hormone and insulin-like growth factor I concentrations remained high, octreotide therapy was begun in October 1992. Two months later, the patient was hospitalized because of a psychotic episode. Her ideas became complex, and she described emotions stemming from what she perceived to be a direct experience of God. She displayed increased energy and interest in the environment. Octreotide was withdrawn and treatment with lithium carbonate was begun to control these psychiatric symptoms.

The patient's symptoms remained stable for 12 years, but octreotide therapy was reinitiated at a different institution in September 2004 because her plasma growth hormone and insulin-like growth factor I levels were persistently elevated. Two months later, the patient was again readmitted for a new crisis of mania. After the dose of lithium carbonate was increased and octreotide was withdrawn, the psychiatric symptoms were again controlled.

Discussion: Psychotic reactions may develop as a rare side effect of dopamine agonists in patients with no history of psychiatric disorders (1). In this patient, symptoms waxed and waned 2 times after treatment with octreotide. We think that use of this somatostatin analogue may have precipitated the manic episodes because increased cerebrospinal somatostatin concentrations have been described in patients with similar symptoms (4). In addition, genetic polymorphisms in somatostatin receptors have also been reported to be associated with bipolar affective disorders. Some of these polymorphisms are present in less than 5% of the general population (5).

Conclusion: We are unaware of previous cases of manic episodes that were precipitated by administration of a long-acting somatostatin analogue. The appearance of psychiatric symptoms after treatment with octreotide suggests that some susceptible individuals show increased sensitivity to somatostatin.

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CORRECTIONS

Correction: Meta-Analysis: Antibiotic Prophylaxis Reduces Mortality in Neutropenic Patients

A recent review regarding antibiotic prophylaxis in neutropenic patients (1) contained an error. Figure 1 should have reported that 106 randomized trials were evaluated for inclusion.

Reference

1. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med*. 2005;142:979-95. [PMID: 15968013]

Correction: Update in Infectious Diseases

In the recent Update in Infectious Diseases (1), the second sentence in the second paragraph of the review of Fritsche and colleagues' study (2) should have read as follows: "These included 1881 strains of MRSA, 1111 strains of coagulase-negative methicillin-resistant *Staphylococcus* species, 122 strains of vancomycin-resistant *Enterococcus* species, 232 strains of penicillin-resistant *Streptococcus pneumoniae*, 249 strains of β -lactamase-positive *Haemophilus influenzae*, and 474 strains of *Moraxella catarrhalis*."

References

1. Bartlett JG. Update in infectious diseases. *Ann Intern Med*. 2006;144:49-56. [PMID: 16389254]
2. Fritsche TR, Kirby JT, Jones RN. In vitro activity of tigecycline (GAR-936) tested against 11859 recent clinical isolates associated with community-acquired respiratory tract and gram-positive cutaneous infections. *Diagn Microbiol Infect Dis*. 2004;49:201-9. [PMID: 15246511]