Modes of Transmission of Hemorrhagic Fever

To the Editor: In their Consensus Statement on hemorrhagic fever viruses that may be used as biological weapons, Dr Borio and colleagues[1] state, "There are no reported cases of person-to-person or nosocomial spread of flaviviruses." At least 2 cases of nosocomial transmission of dengue (a flavivirus) have been reported in the medical literature: one through a needlestick injury[2] and the other through bone marrow transplantation.[3] These events, although rare, suggest that nosocomial spread may also be possible for a more feared flavivirus—yellow fever.

José G. Rigau-Pérez, MD, MPH
Dengue Branch, Division of Vector-Borne Infectious Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
San Juan, Puerto Rico

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2. de Wazières B, Gil H, Vuitton DA, Dupond JL. Nosocomial transmission of dengue from a needlestick injury. *Lancet*. 1998;351:498.
3. Rigau-Pérez JG, Vorndam AV, Clark GG. The dengue and dengue hemorrhagic fever epidemic in Puerto Rico, 1994-1995. *Am J Trop Med Hyg*. 2001;64:67-74.

To the Editor: In their Consensus Statement, Dr Borio and colleagues[1] briefly mention Kyasanur Forest disease virus (KFDV), which occurs in a remote part of the world. In 1957, 2 of my colleagues and I were accidentally infected with KFDV while engaged in vaccine preparation.[2] Despite our adherence to all of the then-current laboratory precautions, including wearing a face mask, face shield, and gown and working in individual vented cubicles, emulsification of infected tissues created an aerosol that resulted in clinical illness. This incident is evidence that KFDV, although transmitted in nature by a tick bite, is indeed infectious as an aerosol.

Our effort (and risk) in 1957 was to prepare a vaccine to protect people living in the region of the Kyasanur Forest (India) from becoming infected. So, many years later, it is very sad that our current concern pertains to the potential peril of KFDV and similar viruses as agents of bioterrorism.

Leonard J. Morse, MD
Departments of Clinical Medicine and Family Medicine and Community Health
University of Massachusetts Medical School
Worcester

1. Borio L, Inglesby T, Peters CJ, et al Hemorrhagic fever viruses as biologic weapons: medical and public health management. *JAMA*. 2002;287:2391-2405.
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In Reply: We agree with Dr Rigau-Pérez that transmission of dengue by needlestick injury and bone marrow transplantation is possible. We excluded dengue from our analysis for reasons we discussed in our article. Although cases of nosocomial transmission of yellow fever have not been reported, it would be prudent to assume that exposure to a viremic patient through needlestick injury or bone marrow transplantation could transmit infection.

In response to Dr Morse, we stated that all of the viruses we reviewed are "highly infectious in the laboratory setting and may be transmitted via small-particle aerosol," as exemplified by his own unfortunate experience. This is why these viruses are routinely handled only in biosafety level 4 laboratories. Such infectivity poses great problems for patient care in the event of an outbreak. We favor the use of point-of-care analyzers to process clinical specimens of patients at the bedside, thereby precluding the need for aerosol-generating procedures and exposure of laboratory workers. In the event that point-of-care analyzers are not available or feasible, we suggest additional precautions to reduce the risk of accidental infection of laboratory workers.

Luciana Borio, MD
Johns Hopkins Center for Civilian Biodefense Strategies
Johns Hopkins Schools of Medicine and Public Health
Baltimore, Md
Critical Care Medicine Department
Clinical Center
National Institutes of Health
Bethesda, Md

Nesiritide vs Nitroglycerin for Decompensated Congestive Heart Failure

To the Editor: Dr Young and the Vasodilation in the Management of Acute [congestive heart failure] CHF (VMAC) investigators[1] found that, among patients with decompensated CHF, nesiritide resulted in only a 2-mm improvement in pulmonary capillary wedge pressure (PCWP) compared with nitroglycerin and a 4-mm improvement compared with placebo at both 3 and 24 hours. Although they claimed nesiritide improves hemodynamic function, this small change is of no clini-

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

cal significance. Subjective dyspnea, as well as all other parameters, were not different between the groups. At 7 days, there were 4 deaths in the nesiritide group and 1 death in the nitroglycerin group, as well as a 4% greater 6-month mortality with nesiritide. The similar baseline characteristics argue against the differences being due to sicker patients randomized to nesiritide. Another recent study of nesiritide[2] also showed minimal improvement, but in the presence of significant and persistent hypotension.

As a clinician, I welcome new advancements in the treatment of heart failure. There is still insufficient evidence to suggest that we should replace existing therapy. Until that proof exists, it would be premature to dismiss an effective treatment (nitroglycerin) before a clearly superior alternative has been demonstrated.

Scott Dunavant, MD
Department of Emergency Medicine
St Joseph Hospital
Lexington, Ky

1. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531-1540.
2. Colucci WS, Elkayam U, Horton DP, et al, for the Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med*. 2000;343:246-253.

To the Editor: I have 3 concerns about the study by Dr Young and the VMAC investigators.[1] First, patients were not adequately randomized. Six (32%) of the 19 baseline characteristics in Table 1 are statistically and perhaps clinically significantly different between treatment groups. These include underlying clinical status, such as baseline use of intravenous pressors (2.5-fold difference between groups). The authors did not address or control for such variation other than to state that the primary outcome, greater reduction in PCWP in the nesiritide group, was also found in patients who were not receiving pressors at baseline. Although pressor use may not have directly confounded the results, it is still likely that the 2 treatment groups were not equivalent.

Second, the VMAC investigators do not provide baseline characteristics of the group that underwent right heart catheterization. Given that the primary finding of the study concerned only patients who were catheterized and that assignment to catheterization was not random, but based on clinical judgment, presentation of such variables would be important in assessing validity and generalizability.

Finally, the investigators' conclusion that nesiritide improves both hemodynamic, as well as self-reported symptoms, seems unwarranted. They do not present any statistically significant data demonstrating nesiritide's superiority in terms of clinical outcomes. They do mention (data not shown) that differences in scores on one scale were significant in a 2-way analysis, but not in the nonparametric analysis presented in Figure 3. A more conservative interpretation of the data would be that while nesiritide did lower PCWP more effectively than did nitroglycerin, this is of unknown importance especially as there was no demonstration of improved clinical outcomes. Likewise, it will be important to assess (in studies with enough power to assess adverse events) the trend toward higher 6-month mortality in the nesiritide group (25.1% vs 20.8%).

William Rifkin, MD
Department of Medicine
Maimonides Medical Center
Brooklyn, NY

1. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531-1540.
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In Reply: We agree with Dr Dunavant that no single clinical trial should be considered in isolation. We point out that another study[1] has found that nesiritide is safe and effective in improving hemodynamics, specifically PCWP and pulmonary artery pressures in patients with decompensated CHF. Our trial, as well as the earlier report by Colucci et al,[1] demonstrated that nesiritide led to rapid reduction in PCWP, which is directly related to improvement of CHF symptoms. Indeed, in our trial, nesiritide consistently was associated with a greater decrease in PCWP during the first 24 hours than nitroglycerin at all time points except at 2 hours.

We disagree with Dunavant's view that the decrease in PCWP was "of no clinical significance." The mean decrease from baseline in PCWP at 3 hours was almost 6 mm Hg. This degree of hemodynamic change is statistically significant when compared with the placebo and nitroglycerin groups and also usually clinically significant in patients with decompensated CHF. It is also important that, unlike nitroglycerin, nesiritide did not induce tolerance. The previous study[1] has, however, demonstrated that higher doses of nesiritide provided even greater reductions in PCWP and pulmonary artery pressures. Nesiritide also had a more rapid onset of clinical effects and proved to be easier to use than nitroglycerin because dose titration was not generally required. Dunavant's comment regarding "significant and persistent hypotension" with nesiritide referred to the previous study,[1] which used doses 150% to 300% greater than the dose in our trial. At the recommended dose,[2] which we used, hypotension occurred with a similar frequency as observed with nitroglycerin during the first 24 hours of dosing with symptomatic hypotension—4% in the nesiritide group and 5% in the nitroglycerin group.

In response to Dr Rifkin, it is not unusual for clinical trials to have some imbalance in a few baseline parameters when treatment groups are compared. If anything, the group receiving nesiritide appeared to have more severe CHF. Because of space constraints, we could not present the specific baseline characteristics of the group stratified by the results of right heart catheterization. However, in this cohort, baseline characteristics were not significantly different between nitroglycerin, nesiritide, and placebo groups with the exception of slightly more patients in

the placebo group having a history of frequent premature ventricular contractions.

Dunavant and Rifkin also comment on issues related to mortality and longer-term clinical outcomes. These are important end points, but our study was not designed as a mortality study (either short-term or long-term). We did point out that there was no statistically significant difference in mortality rates at either the 7-day or 6-month follow-up and that the confidence intervals overlap for this observation. Nesiritide does not appear to be associated with atrial or ventricular arrhythmias.[3] This may translate into improvements in mortality, and such a study would be valuable.

Finally, we believe that our study results are applicable to managing hospitalized patients with CHF. We did not exclude patients who are usually eliminated from such trials (such as patients with CHF due to ischemic events or diastolic dysfunction) and allowed aggressive concomitant heart failure therapy, such as parenteral diuretics, other vasodilators (except nitroglycerin), and even inotropic agents if appropriate.

James B. Young, MD
Heart Failure and Cardiac Transplant Medicine
Cleveland Clinic Foundation
Cleveland, Ohio

Financial Disclosure: Dr Young is a consultant for Scios Inc.

1. Colucci WS, Elkayam U, Horton DP, et al, for the Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Eng J Med.* 2000;343:246-253.
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Preoperative β-Blockade and Risk of Postoperative Atrial Fibrillation

To the Editor: In their study on the effect of preoperative β-blocker therapy on coronary artery bypass graft (CABG) surgery outcomes, Dr Ferguson and colleagues[1] did not address its effect on the incidence of postoperative atrial fibrillation (AF). Atrial fibrillation has been reported in 5% to 40% of patients undergoing CABG,[2] is associated with increased length of hospital stay[3] and increased incidence of perioperative stroke,[4] and generally occurs 2 to 3 days after CABG and seldom earlier.[5] Although a meta-analysis of randomized controlled trials in 1991 showed that prophylactic β-blocker therapy had a protective effect against the development of postoperative AF,[6] its routine preoperative use is still not universally adopted. Furthermore, it would be interesting to know if the trend toward a decrease in stroke that Ferguson et al observed among patients treated with β-blockers was due to a decreased incidence of postoperative AF.

Tsung O. Cheng, MD
Department of Medicine
George Washington University Medical Center
Washington, DC

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In Reply: The direct effect of preoperative β-blocker therapy on postoperative AF is perhaps more complex that it first appears, for several reasons. First, while randomized controlled trials have documented the beneficial effect of β-blockade for prevention of AF,[1,2] in clinical practice patients may receive β-blockers for reasons other than either preoperative or postoperative arrhythmia prevention. They may also have an unrelated contraindication to the drug. Second, several of these trials have shown that patients who receive β-blockers preoperatively, but who do not have β-blockade restarted postoperatively, have an increased incidence of postoperative arrhythmias.[2] Third, it can sometimes be difficult to discriminate whether some antiarrhythmic drugs are administered for prophylaxis, therapy, or both.

We do not have complete information on postoperative antiarrhythmic medications, including postoperative β-blocker therapy. In addition, information about postoperative AF was inconsistently collected due to differences in definition interpretation (duration and documentation). For these reasons, we did not report on the relationship between preoperative β-blocker therapy and postoperative AF incidence.

However, we agree with Dr Cheng that a potential reduction in postoperative AF could be an additional reason beyond the potential reduction in operative mortality[3] to prescribe preoperative β-blocker therapy. The complex relationship among preoperative β-blocker therapy, adverse neurologic outcome following CABG, and incidence of postoperative AF will need to be evaluated in the setting of a randomized trial of preoperative β-blocker therapy in CABG.

T. Bruce Ferguson, Jr, MD
Departments of Surgery and Physiology
Louisiana State University Health Sciences Center
New Orleans

Laura P. Coombs, PhD
Eric D. Peterson, MD, MPH
Duke Clinical Research Institute
Durham, NC

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RESEARCH LETTERS

Cognitive Measures of Vietnam-Era Prisoners of War

To the Editor: Although some studies have found decreased cognitive performance in repatriated prisoners of war (POWS),[1,2] other studies have not found such deficits.[3,4] Many of the studies that have found an intellectual decrement in POWs have methodological limitations, including failure to control for concurrent depression, posttraumatic stress disorder, or other mental illness; nonrandom selection of participants who were unmotivated to malinger; lack of a control group; and insufficient matching between POWs and controls.[4] In contrast, the largest investigation,[3] which studied more than 2500 World War II and Korean War POWs, noted that evidence of organic brain syndrome was "conspicuously absent" from the diagnoses differentiating POWs from controls. More recently, no cognitive differences were found on any cognitive test or on the computed axial tomography scans of POWs and controls.[4] We assessed the relative cognitive status of US Navy Vietnam-era POWs using data gathered by the Naval Operational Medicine Institute's ongoing POW research program.

Methods. Case subjects were 138 naval aviator POWs who were repatriated from North Vietnam in 1973. In 1976, the Navy invited 138 control subjects to participate in the annual examination program. The controls were matched for age, year of commission, job code, education level, marital status, rank, number of flight hours, type of aircraft flown, and specific months flying combat missions. Informed consent was obtained prior to participation.[5] During some years' annual examinations, cognitive assessment was also included.

Performance was compared between POWs and controls on 3 cognitive batteries: the Halstead-Reitan Neuropsychological Battery (HRNB), the Wechsler Adult Intelligence Scale (WAIS), and the CogScreen-Aeromedical Edition (AE). Although all POWs did not complete all 3 tests, each control was administered the same tests as his matched POW. The cases that had both matched-pair members with data on any of the 7 administrations of the 3 tests (117 matched pairs) were included in the study. Differences between groups and test sessions were assessed by multivariate analysis of variance. To assess whether POWs differed from controls on depression, the Minnesota Multiphasic Personality Inventory (MMPI) D score, which was obtained in the same testing session as the cognitive tests, was analyzed using an independent groups *t* test procedure. All analyses were conducted using SPSS v10.1.0 (SPSS Inc, Chicago, Ill).

Results. A comparison of the POWs and controls on 11 demographic variables revealed only 1 significant difference, with the control group having a mean of 0.4 more years of education (15.7 vs 16.1; $P=.03$). The results of the MMPI D score analyses indicated the groups did not differ significantly on depression except for the subgroup that completed the CogScreen-AE. The POW group had a significantly higher D score (20.00 vs 17.67; $P=.002$). There were no significant differences in baseline characteristics, however, between either POWs or controls who did or did not complete the CogScreen AE. However, both group means were well below the score differentiating clinical depression from normal variability.

Problems with colinearity, missing data, or inadequate sample sizes led to exclusion of 14 subtests of the HRNB. Multivariate results using the remaining 9 subtests indicated significant differences ($P<.001$) between cases and controls, with controls having worse performance on 6 of the 9 subtests.

Analysis of WAIS data revealed a significant difference in average scores (129.9 vs 128.4; $P=.048$) between POWs and controls, as well as significant differences between the test sessions for both groups but no interaction. In both digit-span and picture completion subtests, POWs performed better than controls. Univariate tests revealed significant between-session differences for arithmetic, vocabulary, picture completion, and block design, with performance improving over time.

Results of initial multivariate analysis of 64 CogScreen-AE subtests showed no significant between-group difference. A more detailed presentation of these results is available.[6]

Comment. The few statistically significant differences between repatriated POWs and controls showed better intellectual functioning in the POWs. The failure to find a significant decrement in POWs was likely not due to lack of statistical power. Although it is possible that the sample size had insufficient power to detect real differences between groups, the very small observed differences suggest that such an effect would not be of a large magnitude. The direction of the means suggested that the POWs may have slightly better intellectual performance than their matched controls.

Diane Williams, PhD
Susan M. Hilton, MA
Naval Health Research Center
San Diego, Calif

Jeffrey Moore, PhD
Naval Operational Medicine Institute
Robert E. Mitchell Center for Prisoner of War Studies
Pensacola, Fla

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Disclaimer: The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US Government. Approved for public release; distribution unlimited. This research has been conducted in compliance with all applicable Federal Regulations governing the protection of human subjects in research.

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Heart Rate Variability During the Week of September 11, 2001

To the Editor: Catastrophes such as war or earthquake are known to result in increased incidence of sudden cardiac death among survivors, but the physiological mechanisms remain unknown.[1,2] The events of September 11, 2001, produced psychological distress among large numbers of people who were not physically affected by them. We hypothesized that such stress may lead to autonomic dysfunction, which may be reflected in changes in heart rate variability (HRV). Diminished HRV is associated with an increased incidence of cardiovascular and sudden death in patients both with and without coronary artery disease (CAD).[3,4]

Methods. We measured HRV in 12 patients at the Yale-New Haven Hospital who wore 24-hour ambulatory heart monitors during the week of September 11, as well as 12 in control patients who had worn monitors in the preceding 2 months. Control patients were matched for age (within 10 years), sex, presence of CAD or congestive heart failure, and diabetes. Two patients in each group were using β-blockers. Indications for monitoring included palpitations (4 cases, 4 controls), history of or risk for arrhythmia (6 cases, 5 controls), and syncope (2 cases, 3 controls). All patients had been scheduled for heart monitoring prior to September 11. This study was approved by the Yale Human Investigation Committee.

Frequency domain indices of HRV were analyzed using standard power spectrum analysis methods. After editing the R-R interval file to remove ectopic beats and noise, gaps were estimated by interpolated linear splines (recordings with >20% interpolation excluded). The heart rate power spectrum was computed through Fast Fourier Transform and integrated over 5 discrete frequency bands, with high frequency defined as 0.15 to 0.40 Hz.[3] Indices of HRV were log-normalized and compared by paired *t* test.

Results. The logarithm of high-frequency power (a measure of parasympathetic tone) was lower in the subjects monitored after September 11 than in controls (5.54 vs 6.23, $P=.047$). High-frequency power was lower in 9 of the 12 cases compared with their controls ($P=.045$). Mean heart rate did not differ between groups (R-R interval: 857 milliseconds [cases] vs 829 milliseconds [controls], $P=.64$).

Comment. We found a decrease in parasympathetic tone during the week of September 11, 2001, which may represent a physiological perturbation among individuals exposed to large-scale psychological stress. Unlike previous studies in which subjects were directly affected by war or natural disaster,[1,2] the stress experienced by subjects in our study was purely psychological. It is not yet known whether there was increased cardiac mortality or morbidity as a result of the September 11 attacks. Mental stress can induce coronary ischemia[2] and can facilitate lethal arrhythmias.[5] These changes in cardiac blood flow and rhythm may in turn be caused by alterations in autonomic nervous system function.[6] Our data demonstrate that the September 11 attacks may have produced similarly decreased parasympathetic output, which may increase susceptibility to lethal arrhythmias.[7]

Rachel Lampert, MD
Suzanne J. Baron, BA
Craig A. McPherson, MD
Forrester A. Lee, MD
Department of Internal Medicine
Yale University School of Medicine
New Haven, Conn

1. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med*. 1996;334:413-419.
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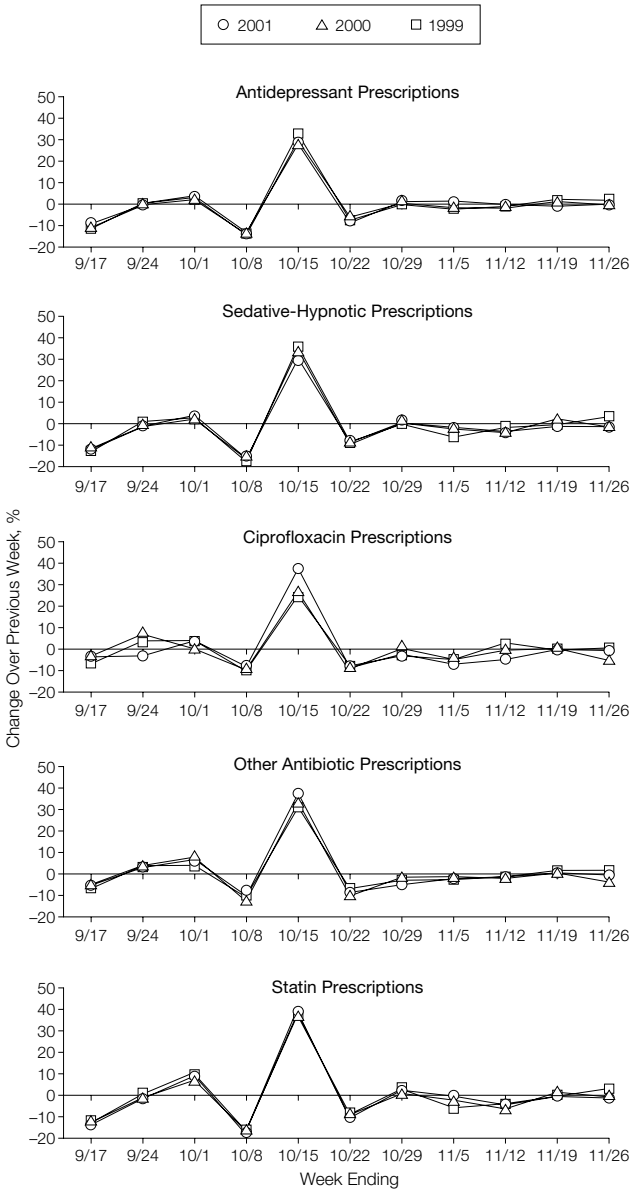
Trends in Drug Prescriptions Among Elderly Residents of Ontario in the Weeks After September 11, 2001

To the Editor: Many residents of Manhattan appear to have experienced symptoms of acute posttraumatic stress and depression following the September 11, 2001, attack,[1] similar to those experienced by survivors of other terrorist attacks and natural disasters.[2,3] Following the events of September 11 and the ensuing anthrax infections, a survey found that 1 in 4 Ca-

nadians was "always or often stressed and overwhelmed," and that 4% reported visiting a health professional to help cope with their reaction to the events.[4]

Such events may be reflected in use of prescription medications. For instance, 29% of long-term evacuees following a volcanic eruption received prescriptions for psychotropic drugs.[5] Insomnia, for which benzodiazepines may be prescribed, is known to occur after local or distant disasters,[6] and one survey found that 11% of US citizens reported having difficulty sleeping in the days following September 11.[7] We examined changes in the frequencies of related drug prescriptions among elderly residents of Ontario in the weeks following the September 11 attacks.

Figure. Trends in Drug Prescriptions in the Weeks After September 11, 1999-2001



Methods. We studied claims for antidepressants, sedatives, and antibiotics submitted to Ontario's universal Drug Benefit program for seniors (ODB), which tracks medication use by all 1.3 million residents of Ontario aged 65 years or older. While prescriptions for psychoactive drugs provide direct evidence of symptomatic anxiety, antibiotics were examined under the hypothesis that, in the absence of documented infections, an increased use was a proxy indicator of anxiety regarding anthrax. We also used prescriptions for lipid-lowering drugs as a comparator.

We examined relative changes in claims volume for each of the 4 medication classes, compared with the previous week, from September 11 to November 26, 2001, and for the same periods 52 and 104 weeks earlier. Secular trends in the use of ciprofloxacin, antidepressants, and lipid-lowering agents necessitated the use of relative changes rather than absolute numbers of prescriptions dispensed. Absolute rates of ciprofloxacin use had declined following the March 2001 introduction of a policy requiring physicians to indicate that it was being used for one of a limited number of indications.

Results. For each medication class, secular changes in number of prescriptions in 2001 were similar to historical trends (Wilcoxon signed rank test on weekly relative change, $P>.45$ for each class) (FIGURE). In all 3 years, the second week of October was associated with a large relative increase in the number of prescriptions. This pattern has been observed historically and has been popularly attributed to relatively large numbers of patients obtaining medication prior to traveling south for the winter. The effect was exaggerated in 2001 for ciprofloxacin, for which we observed an excess of 227 prescriptions over the predicted numbers based on previous years.

Comment. In the 7 days following October 4, 2001, when the first anthrax infection in the United States was reported, we observed an increase in prescriptions for ciprofloxacin despite restrictive new policies that required physicians to indicate an authorized reason for its use. The proportional change in ciprofloxacin prescriptions was unaffected, however, after subsequent anthrax infections were reported in the United States. We did not find any significant changes in the number of prescriptions for antidepressants or anxiolytics.

We acknowledge some limitations to our study. First, because it is limited to prescriptions that were dispensed, it cannot estimate either the number of prescriptions that patients obtained with the intent of filling only if a threat became imminent, or the number of drugs purchased at personal expense. Second, in the case of psychoactive drugs, patients with a history of anxiety may have already had an anxiolytic medication at hand, and thus a sporadic increase in refills would have been difficult to detect. Finally, while pharmacy utilization is a sensitive measure of moderate or severe anxiety or depression, its use is less well established as a marker for mild anxiety or depression.

While Ontarians frequently wait for specialty services, it is unlikely that delays in access to primary care for symptomatic

patients would have influenced our findings. Furthermore, we feel that comprehensiveness of the ODB database counterbalances many of these limitations, as it reflects the experiences of the entire population of Ontarians aged 65 years or older.

Peter C. Austin, PhD
Institute for Clinical Evaluative Sciences
Department of Public Health Sciences
University of Toronto
Toronto, Ontario

Muhammad M. Mamdani, PharmD, MA, MPH
Institute for Clinical Evaluative Sciences
Faculty of Pharmacy
University of Toronto

Liisa Jaakkimainen, MD, MSc, CCFP
Institute for Clinical Evaluative Sciences
Department of Family and Community Medicine
University of Toronto

Janet E. Hux, MD, SM, FRCPC
Institute for Clinical Evaluative Sciences
Department of Medicine
University of Toronto
Clinical Epidemiology and Health Care Research Program
Sunnybrook & Women's College Health Sciences Centre
Toronto

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CORRECTION

Incorrect *P* Value: In the Original Contribution entitled "Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure: A Randomized Controlled Trial" published in the March 27, 2002, issue of THE JOURNAL (2002;287:1531-1540), there was an incorrect *P* value in Table 1. On page 1535, the *P* value should have been .30 for "acute coronary syndrome within 7 days before start of study drug," which is the last entry under the heading "medical history."