

## Issues in Establishing Primary Stroke Centers

**To the Editor:** Dr Alberts and colleagues<sup>1</sup> reported that primary stroke centers should include “acute stroke teams, stroke units, written care protocols, and an integrated emergency response system.” Regrettably, the authors only briefly mentioned the need for rehabilitation to “hasten recovery following stroke.” They reported that only 2% to 3% of patients with stroke receive tissue-type plasminogen activator (tPA) nationwide, but they failed to mention that 31% of patients with stroke require assistance in activities of daily living, 20% require assistance in mobility, and 16% are institutionalized.<sup>2</sup>

The authors described rehabilitation as occurring “after the acute hospitalization and often in facilities remote from the acute care hospital.” However, a consensus panel for poststroke rehabilitation practice guidelines<sup>3</sup> recommended to “begin rehabilitation-oriented care immediately, and increase the patient’s activity as soon as medically feasible during the acute phase,” to “take steps to prevent complications throughout all stages of treatment,” and to “screen the patient for formal rehabilitation during the acute hospitalization.” The omission of these tenets by Alberts et al is glaring. They need to be included as the consensus panel intended.

The authors also concluded that “the trauma center model has important elements that are applicable to stroke centers.” If the authors reviewed guidelines for the care of trauma patients, they would have found that “the rehabilitation of the injured patient should begin during the first hospital day.”<sup>4</sup> While the authors described systematic stroke care within the acute care setting, it clearly was not comprehensive.

For the 4.4 million stroke survivors<sup>2</sup> in the United States, many would agree that administration of tPA should occur within the first 3 hours after a stroke, but that rehabilitation occurs during the remainder of their lifetimes. While stroke centers may decrease mortality and morbidity, the authors should not forget the aftermath with which many stroke survivors live.

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1. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. *JAMA*. 2000;283:3102-3109.

2. American Heart Association. *2000 Heart and Stroke Statistical Update*. Dallas, Tex: American Heart Association; 1999.

3. Gresham GE, Duncan PW, Stason WB, et al. *Post-stroke Rehabilitation: Clinical Practice Guideline No. 16*. Rockville, Md: US Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; May 1995. AHCPR Publication No. 95-0662.

4. Committee on Trauma, American College of Surgeons. Rehabilitation. In: *Resources for the Optimal Care of the Injured Patient: 1999*. Chicago, Ill: American College of Surgeons; 1998:chap 12.

**To the Editor:** Part of the rationale for primary stroke centers, which Dr Alberts and colleagues<sup>1</sup> endorse, is to rapidly

administer tPA to patients experiencing strokes. Alberts discloses that he has financial ties to Genentech Inc, which manufactures tPA.

It would be reassuring if the authors could definitively state that they have no other financial ties to any manufacturer of tPA. It would also be important to state that no expenses of the Brain Attack Coalition have been underwritten by any manufacturer of tPA.

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1. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. *JAMA*. 2000;283:3102-3109.

**In Reply:** Dr Zorowitz points out the importance of early rehabilitation in stroke care, which we certainly support. Early rehabilitation is part of almost every stroke protocol, and we strongly endorse the use of such protocols, as we indicated in our article. In our discussion we also stated our support for early rehabilitation. However, since a significant proportion of poststroke rehabilitation can occur outside of the initial treating hospital, we do not feel that a primary stroke center hospital must necessarily have on-site comprehensive rehabilitation. This would further restrict and reduce the number of hospitals able to provide acute stroke care. The issue of rehabilitation will be addressed in a future article that focuses on comprehensive stroke centers.

In terms of Dr Helmer’s concerns about financial ties between the authors and Genentech Inc, only Dr Alberts (as stated in the article) has financial ties to the company, a manufacturer of tPA. Genentech Inc has had no role whatsoever in the development of the stroke center article or in the operations or expenses of the Brain Attack Coalition.

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**GUIDELINES FOR LETTERS.** Letters discussing a recent *JAMA* article should be received within 4 weeks of the article’s publication and should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 500 words and 6 references. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors as space permits and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Letters will not be returned unless specifically requested. Also see Instructions for Authors (July 5, 2000). Letters may be submitted by surface mail: Letters Editor, *JAMA*, 515 N State St, Chicago, IL 60610; e-mail: JAMA-letters@ama-assn.org; or fax (please also send a hard copy via surface mail): (312) 464-5824.

**Letters Section Editors:** Stephen J. Lurie, MD, PhD, Senior Editor; Phil B. Fontanarosa, MD, Executive Deputy Editor.

## Safety Precautions to Limit Exposure From Plague-Infected Patients

**To the Editor:** Dr Inglesby and colleagues<sup>1</sup> recommend that aerosol-generating autopsies (essentially all autopsies) performed on individuals who have died of plague should be conducted in negative-pressure rooms by prosectors wearing high-efficiency particulate air-filtered respirators. However, their recommendation points to a major limitation in our national autopsy infrastructure. Deaths from known bioterrorist events are classified as homicides and therefore fall under the jurisdiction of medical examiners and coroners, who would investigate these deaths and, unless overwhelmed by large numbers of fatalities, perform autopsies of the bodies. Similarly, medical examiners or coroners might also perform autopsies of individuals who die precipitously and unexpectedly from a covert bioterrorist attack.

Unfortunately, most offices of medical examiners and coroners and, indeed, most hospital autopsy facilities in the United States are inadequately constructed and ill prepared to perform autopsies that require respiratory precautions. Aerosol-transmitted outbreaks of tuberculosis have been traced to autopsies done in the Syracuse, NY, Medical Examiner's office, Los Angeles, Calif, Coroner's Office, University of Arkansas School of Medicine, and University of Health Sciences/Chicago Medical School.<sup>2-5</sup> These outbreaks were attributed to inadequate ventilation of autopsy rooms and insufficient respiratory precautions.

If autopsy prosectors and other office personnel are not adequately protected from the risks of tuberculosis, it is unlikely that they will be protected from the risk of plague. Many offices of medical examiners and coroners are located in older facilities, which often have common air circulation between prosecting areas and administrative spaces. Prosectors often do not adhere to guidelines intended to prevent the spread of blood-borne and aerosolized pathogens. To perform safe autopsies on bodies with infectious diseases, including those infectious diseases that may be a consequence of bioterrorism, we need an improved national autopsy infrastructure. Funding is needed to bring autopsy facilities into compliance with accepted public health standards and to provide prosectors with appropriate protective equipment. Prosectors will need to comply with recommended safety procedures. Because the infective potential of a body may be unknown, all autopsy-performing agencies consistently should be able to protect both prosectors and office personnel from aerosolized pathogens.

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1. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. *JAMA*. 2000;283:2281-2290.
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transmission of *Mycobacterium tuberculosis* at the bedside and during autopsy. *Ann Intern Med*. 1995;122:922-925.

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**To the Editor:** Dr Inglesby and colleagues<sup>1</sup> recommend isolation of patients with pneumonic plague to prevent droplet (usually defined as particles larger than 5  $\mu$ ) transmission. Isolation of this type only includes the use of surgical masks when standing within 1 m of the patient (because large droplets do not settle beyond 1 m of the patient) and no special ventilation systems.<sup>2</sup> However, if airborne particles are aerosolized (ie, are smaller than 5  $\mu$ ), then well-ventilated rooms under negative pressure and 95% efficient masks (class N95 respirators) would be required, as is the case for pulmonary tuberculosis.<sup>2</sup>

Inhaled aerosols are not trapped by the mucociliary defenses of the respiratory tract and can penetrate to the periphery of the lung where they implant, proliferate, and become pathogenic. Indeed, from extensive autopsy data in the 1910-1911 Manchurian outbreak of pneumonic plague, the most common lesion was alveolitis, rather than involvement of the mucous membranes of the upper respiratory tract.<sup>3,4</sup> Involvement of these airway sites, with secondary cervical buboes, would be expected if particles larger than 5  $\mu$  were inhaled and deposited on the sticky mucus stream moving over the upper respiratory tract and larger airways to the oropharynx. These sites have been noted occasionally to be infected in other outbreaks of pneumonic plague<sup>5</sup>; they are routinely infected if plague bacilli are implanted in the oral cavity of experimental animals, whereas primary plague pneumonia develops if the bacilli are injected directly into the trachea.<sup>2,5</sup> Both droplet and aerosol transmission in several outbreaks of pneumonic plague have occurred; large particles that are inhaled are likely to lodge in the upper respiratory tract and produce tonsillar plague, whereas droplet nuclei tend to lodge in the lung and give rise to primary plague pneumonia.<sup>5</sup>

To prevent the spread of an almost uniformly fatal disease like primary plague pneumonia, it seems prudent to apply the more stringent standard of care, eg, use of well-ventilated rooms with negative pressure for housing patients and class N95 respirators by health care workers. To strengthen US preparedness against bioterrorism, we must rethink existing recommendations to ensure an adequate response to potential public health disasters.

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1. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. *JAMA*. 2000;283:2281-2290.
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5. Meyer KF. Pneumonic plague. *Bacteriol Rev*. 1961;25:249-261.

**In Reply:** The authors from the Working Group for Civilian Biodefense share Dr Nolte's concerns about the potential limitations of the national autopsy infrastructure to prevent postmortem-associated acquisition of infection. As Nolte points out, guidelines regarding pathogens that might be aerosolized by postmortem procedures are of importance not only to protect against disease caused by biological weapons, but also to prevent the spread of naturally acquired infectious diseases.

Dr Levison proposes that infection control guidelines for patients with pneumonic plague should recommend negative pressure rooms for affected patients and class N95 respirators for health care workers. While data are limited and further research would be useful, there is no epidemiological evidence that pneumonic plague can be spread from person to person by droplet nuclei (aerosols). This is in contrast to pulmonary tuberculosis, for which there is clear evidence of contagion by droplet nuclei. Available evidence suggests that the risk of person-to-person spread of pneumonic plague is very low and that it requires respiratory droplet transmission by direct close (<2 m) contact.

The last US case of person-to-person spread of pneumonic plague was in a 1924 epidemic during which the disease was spread from 2 index patients to a number of close household contacts.<sup>1</sup> In the United States in the last 50 years, there have been 7 cases of primary pneumonic plague and 54 cases of pneumonic plague secondary to the bubonic or septicemic form of disease (Centers for Disease Control and Prevention [CDC], D.T.D., unpublished data, July 14, 2000). However, none of these cases resulted in plague being spread from person to person.<sup>2</sup>

In the Manchurian pneumonic plague epidemics of 1910-1911, investigators concluded that disease was spread by respiratory droplets and required close, direct contact with patients; furthermore, they concluded that the use of a simple gauze mask was effective in preventing spread from patients to health care workers.<sup>1,3,4</sup> Despite the continued sporadic occurrence of plague around the world, often in crowded urban settings, there has been a paucity of pneumonic plague outbreaks. There are no modern reports of pneumonic plague outbreaks in which more than 1 generation of pneumonic transmission has occurred.

There is no evidence to warrant the use of class N95 masks and negative pressure rooms to interrupt the secondary transmission of pneumonic plague. Moreover, recommending these procedures could lead to counterproductive logistical and cost issues. Class N95 masks are much more expensive than simple surgical masks and would require fit-testing before use. The number of negative pressure rooms in most hospitals is quite limited and adding a substantial number of such rooms would be very costly.

Because of these considerations and the other evidence presented in the working group consensus statement on the management of plague,<sup>5</sup> the working group advises the use of simple surgical masks as part of respiratory droplet precautions to pre-

vent person-to-person transmission of pneumonic plague. This recommendation is consistent with those of the CDC and the Association for Professionals in Infection Control and Epidemiology,<sup>2</sup> as well as that of the World Health Organization expert committee on plague.<sup>6</sup>

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### The Role of Genotypic Resistance Testing in Selecting Therapy for HIV

**To the Editor:** The usefulness of genotype resistance testing in the clinical management of HIV infection is increasingly clear. However, as Dr Hirsch and colleagues<sup>1</sup> state, several technical issues concerning standardization and clinical validation have yet to be resolved.

Although genotypic assays are increasingly common in the clinical setting, interpretation of results is more complex than merely identifying mutations and then eliminating antiretroviral drugs that supposedly are not efficacious. In fact, the same combinations of primary and secondary mutations may result from several different scenarios.

Genotypic testing shows the mutational pattern detected in the amplicon. This does not necessarily correspond to a single viral clone because the same pattern may result from the superimposition of the genotypes from different clones. It may be quite misleading to assume that all mutations belong to the same clone, as is often done in a more conservative therapeutical approach. On the other hand, given the low limit of detection for small viral populations and the known association of some primary and secondary mutations, it is unlikely that each mutation represents a separate viral clone. Intermediate interpretations could explain discordant clinical results in patients with similar genotypic resistance patterns. Unfortunately, identification of different clones in the amplicon is too costly and laborious to be included in current protocols.

At present, we feel that genotypic techniques should be considered as an additional tool in HIV therapy. However, their use should occur in a wider context that includes treatment history, clinical history, and adherence expectations. Although phenotypic assays are more costly and laborious, they are probably more useful because they directly express the degree of sensitivity of the main circulating population to the drugs. Phenotypic techniques are also familiar in that they resemble routine bacterial sensitivity studies and, furthermore, allow clinicians to estimate the inhibitory quotient for antiretroviral drugs.

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1. Hirsch MS, Brun-Vézinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAMA*. 2000;283:2417-2426.

**In Reply:** We have previously addressed the issues raised by Drs Pérez-Molina and Fernández.<sup>1</sup> As we have stated, resistance testing (genotypic as well as phenotypic) should be viewed in the context of many other factors when choosing drug therapy. Such factors include treatment history, viral load, medication tolerance, adherence, and concomitant medical conditions. Pérez-Molina and Fernández raise a theoretical concern regarding linkage of mutations that we have discussed previously<sup>1</sup> and that may apply to phenotyping as well as genotyping.

Available data suggest that colinearity of mutations is common in some settings.<sup>2</sup> The conclusion of Pérez-Molina and Fernández that phenotypic tests are "more useful" is premature based on current evidence. The relative utility of genotyping and phenotyping will be determined by ongoing and future trials, as well as by clinical practice.

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1. Hirsch MS, Conway B, D'Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection: implication for clinical management. *JAMA*. 1998;279:1984-1991.

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## RESEARCH LETTERS

### The Continuing Epidemic of Obesity in the United States

**To the Editor:** Obesity is a major cause of morbidity and mortality in the United States.<sup>1</sup> Each year, an estimated 300 000 US adults die of causes attributable to obesity.<sup>2</sup> Obesity also substantially increases morbidity and impairs quality of life.<sup>3</sup> Overall, the direct costs of obesity and physical inac-

tivity account for approximately 9.4% of the national health care expenditures in the United States.<sup>4</sup> Last year, we reported that the prevalence of obesity (defined as body mass index  $\geq 30$  kg/m<sup>2</sup>) based on self-reported weight and height in US adults increased from 12.0% in 1991 to 17.9% in 1998.<sup>5</sup> To determine whether this increase is continuing, we examined 1999 data from the Behavioral Risk Factor Surveillance System (BRFSS).

**Methods.** The BRFSS is a cross-sectional telephone survey of noninstitutionalized civilian adults aged 18 years and older conducted by the Centers for Disease Control and Prevention and state health departments.

The BRFSS questionnaire primarily includes questions about personal behaviors that increase risk for 1 or more of the 10 leading causes of death in the United States. The BRFSS uses a multistage cluster design based on random digit dialing methods of sampling to select a representative sample from each state's noninstitutionalized civilian residents aged 18 years and older. Data collected from each state are pooled to produce nationally representative estimates. We used data on self-reported weight and height to calculate BMI as weight (kg) divided by height (m<sup>2</sup>). The SAS (version 6.09; SAS Institute, Cary, NC) and SUDAAN (version 7.5; Research Triangle Institute, Research Triangle Park, NC) software programs were used in the analyses and to account for the complex sampling design.

**Results.** In 1999, obesity continued to increase in men and women across all sociodemographic groups and all regions of the United States (TABLE). The prevalence of obesity increased significantly from 17.9% in 1998 to 18.9% in 1999, an increase of 5.6% in 1 year and of 57% from 1991. Average weight increased from 76.2 kg in 1998 to 76.7 kg in 1999 (84.4 kg to 85.0 kg among men and 68.4 kg to 68.7 kg among women). In 1991, 4 of the 45 participating states had obesity rates of 15% or greater, whereas by 1999, 39 states had rates of 15% or greater. In 1991, none of the 45 participating states had obesity rates of 20% or greater; however, by 1998, such rates were seen in 7 states and in 1999, in 16 states.

**Comment.** This continuing trend in obesity is a critical public health threat in the United States. Clearly, genes related to obesity are not responsible for the epidemic of obesity because the US gene pool did not change significantly between 1991 and 1999. We have recently reported a 33% increase in diagnosed diabetes from 1990 to 1998.<sup>6</sup> This increase was highly correlated with obesity, and this emphasizes that obesity is not just a cosmetic disorder but a major risk factor for chronic diseases.

Unfortunately, the prevalence of obesity is likely to continue increasing in the years ahead. The time has come to develop a national, comprehensive plan to prevent and treat the obesity epidemic. The general goals are to prevent further weight gain in individuals with normal weight or overweight, reduce body weight among obese and overweight individuals, and encourage individuals to maintain a lower body weight over the long term. The approach should develop appropriate

**Table.** Increase in Obesity Prevalence Among Adults, by Selected Characteristics, 1998 to 1999

Characteristic	1998, % (SE)	1999, % (SE)
Total	17.9 (0.17)	18.9 (0.18)
Sex		
Men	17.7 (0.25)	19.1 (0.27)
Women	18.1 (0.23)	18.6 (0.23)
Age groups, y		
18-29	12.1 (0.34)	12.1 (0.35)
30-39	16.9 (0.35)	18.6 (0.38)
40-49	21.2 (0.41)	22.4 (0.42)
50-59	23.8 (0.51)	24.2 (0.49)
60-69	21.3 (0.53)	22.3 (0.54)
≥70	14.6 (0.42)	16.1 (0.46)
Race/ethnicity		
White	16.6 (0.18)	17.7 (0.19)
Black	26.9 (0.62)	27.3 (0.61)
Hispanic	20.8 (0.74)	21.5 (0.73)
Other	11.9 (0.87)	12.4 (0.79)
Educational level		
Less than high school	24.1 (0.56)	25.3 (0.60)
High school	19.4 (0.30)	20.6 (0.31)
Some college	17.8 (0.32)	18.1 (0.32)
College or above	13.1 (0.27)	14.3 (0.29)
Smoking status		
Never smoked	17.9 (0.24)	19.0 (0.25)
Exsmoker	20.9 (0.36)	21.5 (0.37)
Current smoker	14.8 (0.33)	15.7 (0.33)
Regions		
New England	14.4 (0.43)	14.9 (0.43)
Mid Atlantic	16.7 (0.50)	17.8 (0.51)
East North Central	19.1 (0.43)	20.3 (0.49)
West North Central	18.0 (0.40)	19.0 (0.38)
South Atlantic	18.6 (0.35)	19.3 (0.34)
East South Central	20.0 (0.46)	21.2 (0.47)
West South Central	19.9 (0.51)	21.0 (0.58)
Mountain	14.1 (0.60)	14.5 (0.47)
Pacific	17.0 (0.53)	18.1 (0.54)

interventions to promote improved nutrition and increased physical activity and to identify effective educational, behavioral, and environmental approaches to control and prevent obesity. Such intervention programs should be implemented by health departments and communities throughout the United States.

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### Racial Differences in Knowledge Regarding Hepatitis C Virus Infection

**To the Editor:** Hepatitis C virus infection is the most common chronic blood-borne infection in the United States, with an estimated 2.7 million persons infected.<sup>1</sup> Most infected persons may not be aware of their infection because they are not clinically ill. However, infected persons serve as a source of transmission to others and are at risk of developing chronic liver disease during the first 2 or more decades after infection.<sup>2</sup> To help develop and target prevention messages, we included questions about hepatitis C on a national health survey. Our objective was to determine knowledge regarding hepatitis C virus infection, especially among minorities disproportionately affected.

**Methods.** Healthstyles is a large database of responses to mailed surveys designed specifically for health and lifestyle-related marketing and communication programs. Healthstyles has had more than 2500 respondents annually since 1995 and, in addition to demographic information, includes responses to questions about health behaviors, attitudes, and knowledge. Full details of the methods are published elsewhere.<sup>3</sup> Questionnaires were mailed in June 1999 to 3666 adults who completed a prior, more comprehensive survey for which participants were selected by quota sampling and stratified on demographic variables to represent US adults. Racial/ethnic minorities were oversampled, and weighted analysis was performed using SPSS statistical software (SPSS Inc, Chicago, Ill). Five-point Likert scales were used for responses to most statements.

**Results.** Of 2636 (72% of sample) respondents, 74.6% were white, 11.6% black, and 10.0% Hispanic. Black and white respondents were equally more likely to report at least a high school education (92% than Hispanics (79%). Blacks and Hispanics were more likely than whites to report household incomes less than \$20 000 (41% and 33%, respectively, vs 22%,  $P < .05$ ). Overall, a large proportion of participants responded either inaccurately or with uncertainty to multiple statements regarding hepatitis C virus infection (TABLE). Although blacks were more likely to report having heard of hepatitis C virus than whites or Hispanics (94% vs 89% and 87%, respectively,  $P < .05$ ), blacks were less likely to respond accurately to multiple statements regarding hepatitis C risks and prevention.

**Comment.** This survey indicates that a substantial proportion of adults are either uncertain or inaccurately informed about hepatitis C and that racial differences in knowledge of hepatitis C may exist. Major limitations of this study are that

**Table.** Comparison of Knowledge About Hepatitis C Among Racial/Ethnic Groups Responding to the 1999 Healthstyles Survey\*

Knowledge Item	White (%)	Black (%)	Hispanic (%)
Can be infected by shaking hands with an infected person			
Agree	11.9	21.7†	13.3
Disagree+	57.9‡	45.5	46.6
Neither	30.2	32.9	40.0
There is a vaccine for hepatitis C			
Agree	24.4	35.5†	30.5
Disagree+	27.2	19.5†	24.9
Neither	48.4	45.0	44.6
Someone with hepatitis C virus infection can feel fine			
Agree+	40.4	45.0	44.3
Disagree	9.9	9.3	10.0
Neither	49.6	45.7	45.7
Hepatitis C can cause the liver to stop working			
Agree+	54.7	49.2	50.6
Disagree	40.4	46.6	43.1
Neither	4.9	4.2	6.3
Someone with liver disease should avoid alcohol			
Agree+	71.4	70.5	69.2
Disagree	4.1	8.3†	3.5
Neither	24.5	21.2	27.3
A coworker of someone with hepatitis C virus infection should be tested§			
Yes	45.8	58.9‡	44.9
Someone receiving a blood transfusion in 1999 should be tested§			
Yes	23.6	35.1†	24.7
Someone who currently injects illegal drugs should be tested§			
Yes+	91.2	86.2†	89.2

\*Correct answers are indicated by +. Percentages may not sum to 100 because of rounding.

†Significantly different from whites,  $P < .05$ .

‡Significantly different from both other groups,  $P < .05$ .

§These items were presented as boxes to be checked if respondent felt the person indicated should be recommended for hepatitis C virus testing. "Yes" indicates that the box was checked.

questions about hepatitis were included in a lengthier standardized health survey, and no information is available on whether this format or wording is culturally appropriate for different populations.

The Centers for Disease Control and Prevention, in partnership with voluntary, professional, and other nongovernmental health organizations, is currently expanding efforts to educate the public and health professionals about prevention and control of hepatitis C virus. Studies designed to assess racial and cultural differences in knowledge about hepatitis C and programs to develop, disseminate, and evaluate culturally appropriate prevention and control messages are needed. As blacks are disproportionately affected by hepatitis C infection (estimated prevalence, 3.2% vs 1.5% in whites),<sup>2</sup> it is espe-

cially important for prevention education and activities to be specifically designed and evaluated for effectiveness in this population.

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## Levels of Environmental Endotoxin and Prevalence of Atopic Disease

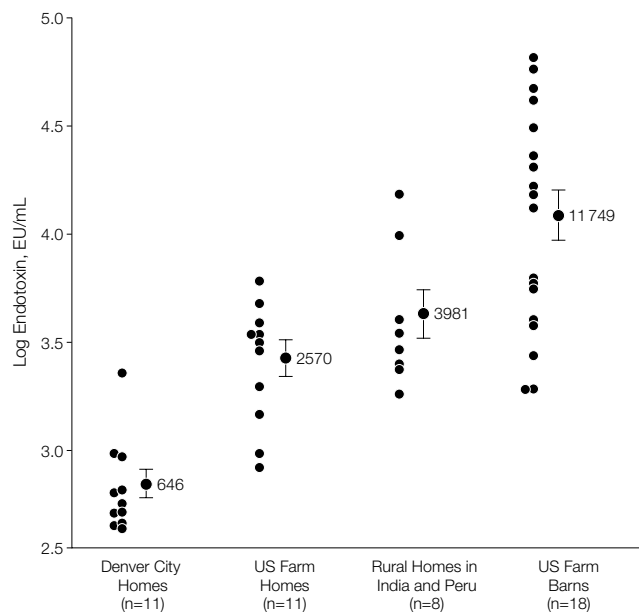
**To the Editor:** While the prevalence of asthma and allergic disease is increasing worldwide,<sup>1</sup> both diseases appear to be less common in rural settings in developing countries and farming communities in industrialized countries.<sup>2</sup> Indeed, some locales seem to be almost free of asthma.<sup>3</sup> To explain the low prevalence of asthma in these settings, the "hygiene hypothesis" suggests that early childhood exposure to high levels of bacterial and viral pathogens leads to a lower risk of asthma and atopy.<sup>4,5</sup> The immune response to these infections would presumably inhibit helper T cell type 2 (T<sub>H</sub>2)-type allergic responses.

We recently reported on the potential of environmental endotoxin—a cell-wall component from gram-negative bacteria that is ubiquitous in the environment—to provide an atopy-protective effect.<sup>6</sup> Infants sensitized to common allergens had significantly lower levels of house-dust endotoxin in their homes. Furthermore, higher house-dust endotoxin levels correlated with increased proportions of interferon- $\gamma$ -producing CD4 T<sub>H</sub>1 lymphocytes in peripheral blood, suggesting that household endotoxin exposure may have an atopy-protective effect by augmenting T<sub>H</sub>1-type immune development. Therefore, we sought to determine if people in locales with a lower prevalence of asthma and atopy have greater exposure to environmental endotoxin.

**Methods.** We measured levels of house-dust endotoxin obtained from homes in 3 different settings: urban homes in Denver; farm homes and associated barns (with animals such as cows, horses, goats, chickens, cats, and dogs) located in Colorado except for 1 pair each in New Hampshire, Wyoming, and Missouri, respectively; and homes in rural India and Peru that are inhabited by similar animals. Methods for house dust collection, preparation, and endotoxin measurement were described previously.<sup>5</sup>

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**Figure.** House-Dust Endotoxin Concentrations From Homes in Denver, US Farms, and Rural Areas of Peru and India



House-dust endotoxin levels are reported in endotoxin units (EU)/mL, using reference standard endotoxin provided by the US Food and Drug Administration. Log transformation of endotoxin values normalized the distribution of the data. Data points with error bars and associated numbers indicate the geometric mean values and SEM for each location subgroup. Wilcoxon rank sum test,  $P < .001$ . Farm barns outnumber farm homes because some homes had more than 1 associated barn and also because some barns were sampled with permission from workers when farm homeowners were not home.

**Results.** Urban homes had significantly lower house-dust endotoxin levels than farm homes and rural homes in developing countries ( $P < .001$ , Wilcoxon rank sum test) (FIGURE). Farm barns had significantly higher endotoxin levels compared with both farm homes ( $P < .001$ ,  $t$  test) and rural homes in developing countries ( $P = .03$ ,  $t$  test). Farm home and associated barn endotoxin levels were significantly correlated (Spearman  $r = 0.67$ ,  $P = .02$ ).

**Comment.** Greater levels of exposure to environmental endotoxin from early childhood, especially in rural areas of de-

veloping countries and in farming communities, may help explain the low prevalence of asthma and allergies observed in children raised in these environments. If environmental endotoxin exposure in early life has an atopy-protective effect, then  $T_H1$ -type activity may be induced separately from exposure to serious infections, thus suggesting a possible strategy for allergy and asthma prevention.

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## CORRECTION

**Incorrect Negative Predictive Value:** In the Original Contribution entitled "The Role of Clinical Suspicion in Evaluating a New Diagnostic Test for Active Tuberculosis: Results of a Multicenter Prospective Trial" published in the February 2, 2000, issue of THE JOURNAL (2000;283:639-645), there were errors in the reporting of 1 negative predictive value. On page 639, in the abstract, under "Results," the last sentence should read "Corresponding negative predictive values were 99%, 91%, and 55% (E-MTD test) vs 96%, 71%, and 37% (AFB smear)." On page 643, the second to last sentence in the first paragraph under the heading "Estimating Clinical Utility" should read "However, the expected NPV of the AFB smear was only 37%, compared with 55% for the E-MTD." On page 644, in Figure 2, the Enhanced *Mycobacterium tuberculosis* Direct Test bar for negative predictive value of high suspicion for tuberculosis (87) should be 55% instead of 91%. Also on page 644, in column 3, the last sentence in the first paragraph should read "The high and consistent specificity of the E-MTD also appeared to be clinically valuable in excluding disease among patients with intermediate CSTB estimates, offering an intermediate NPV of 91%, compared with 71% for AFB smear."