

Risk of HIV Transmission Through Breastfeeding

To the Editor: Dr Miotti and colleagues¹ found a significant decrease in the risk of human immunodeficiency virus (HIV) transmission to infants after 6 months of breastfeeding in Malawi. However, some limitations may have weakened their conclusions.

Whereas the main inclusion criterion was a negative polymerase chain reaction (PCR) result for HIV at 6 weeks of life, more than 25% of the children had tested negatively earlier (lower quartile, 1.4 months). For the many cases estimated to have occurred before 3 months of life (Figure 2, in their article), the first negative PCR result was probably obtained very early, at a minimum of 0.7 months, and the first positive PCR result shortly after. Even by using dried blood spot,² timing of acquisition of HIV infection cannot be ascertained for these children, who were nevertheless considered as cases of postnatal transmission in the analysis. The authors' assumption of underestimation of postnatal transmission during the first semester of life seems therefore unlikely.

No information about the distribution of time intervals between the last negative and the first positive PCR result was provided. These data would have been useful to assess the precision of the estimated date of infection. The circumstances of follow-up may have introduced imprecision in the estimations, especially after 12 months of follow-up.³ Moreover, the authors' Figure 3 suggests a substantial decrease in infection rate after the first year of life rather than after the first 6 months as stated in the text.

The hypothesized relationship between birth weight and quantity of ingested milk can be decreased by the probable increased maturity of intestinal tract and immunological status of the heaviest infants. Also, the relationship suggested by the authors between mastitis and maternal age has not been observed in a comparable population.⁴ More precise data on breastfeeding practices (exclusive or mixed) would have been useful, especially given the findings of recent publications.⁵

Finally, Miotti et al provided interesting information on the risk of HIV transmission through breastfeeding, but their conclusions about the implications of these findings should be moderated. Consequences of artificial feeding and early weaning on infant growth and morbidity are poorly understood. We hope that current studies and pilot programs of reduction of mother-to-child transmission of HIV in Africa will soon provide such data to complement risk estimations of postnatal HIV transmission.⁶

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1. Miotti PG, Taha TE, Kumwenda NI, et al. HIV transmission through breastfeeding: a study in Malawi. *JAMA*. 1999;282:744-749.
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5. Coutoudis A, Pillay K, Spooner E, Kuhn L, Coovadia H, for the South African Vitamin A Study Group. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. *Lancet*. 1999;354:471-476.
6. Leroy V, Newell ML, Dabis F, et al. International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. *Lancet*. 1998;352:597-600.

In Reply: Dr Castetbon and colleagues argue that we may have overestimated the early breastfeeding risk of HIV acquisition because infants were tested too early to exclude a delivery-related transmission of HIV. By design, all infants were older than 4 weeks at the time of the last negative HIV result. By 4 weeks, HIV is detectable in almost all perinatally infected, non-breastfed infants.¹ Hence, it is very unlikely that study infants were infected during delivery.

Our estimate of the breastfeeding infection risk in the first months can only be an underestimate of the true infection risk because any breastfeeding transmission in the first month could not be established. A variety of virologic and immunologic factors and the results of recent studies in Kenya² and Brazil³ support the hypothesis of a high risk of infection from very early breastfeeding.

Visits were scheduled at 1.5 and 3 months, every 3 months to age 18 months, and every 6 months thereafter. The actual time of visits varied, as expected. Infants were grouped in 6-month intervals to provide more stable summary data. As children aged, they were less likely to return for visits. Because of the longer intervals between visits and the small number of infections in later months, infections in the first 6 months were more precisely timed (mean [SD] window of infection, 62 [40] days) than those after 1 year (196 [140] days). In reference to the need for

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Letters Section Editors: Phil B. Fontanarosa, MD, Deputy Editor; Stephen J. Lurie, MD, PhD, Fishbein Fellow.

adjustments in the analysis, the data presented show that the factors we examined did not affect the risk of transmission, thus eliminating the need to adjust for such factors.

Our data on mastitis showed no excess risk, but, as we stated, were limited to the late months of the study. In a separate study by our group, subclinical mastitis was associated with both high viral level in breast milk and transmission to the infant in the early months.⁴ The relationship between mastitis and HIV transmission thus needs further investigation. As to the effect of supplemental feeding on HIV transmission, we presented data showing no significant relationship between transmission and breastfeeding in a time-dependent covariate analysis. A subsequent report by other investigators⁵ about the possible role of supplemental feeding in increasing transmission risk points to the urgent need for further study in this important area.⁶

Breastfeeding issues in areas with high HIV prevalence are complex. Translation from scientific findings to policy outside of a study setting will require a balanced, unbiased review of many factors in diverse circumstances.

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1. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission [review]. *AIDS*. 1995;9:F7-F11.

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Clinical Diagnosis of Carpal Tunnel Syndrome

To the Editor: Dr Atroshi and colleagues¹ reported on the population prevalence of carpal tunnel syndrome (CTS), but their methods and conclusions raise 3 questions.

First, this study addresses patients not hands. Surely there was not 100% concordance between symptoms, physical signs, and nerve conduction studies between the patient's hands. How did the authors analyze data for a patient with bilateral symptoms but unilateral physical findings or nerve conduction studies?

Second, physical findings are notoriously unreliable in the diagnosis of CTS, especially in less severe cases. "Clinically certain CTS" would be more accurately described as "clinically suspected CTS." Furthermore, CTS was defined as either symptoms plus signs, or symptoms plus positive nerve conduction studies. In light of the greater reliability and clinical accuracy of nerve conduction tests,² it would seem prudent to define CTS as symptoms plus positive nerve conduction studies, with or without physical signs.

Third, caution should be used in interpreting the findings on occupational hand use. Because this is a cross-sectional study, cause and effect cannot be inferred between work and CTS, especially in light of the methods, which relied on self-reported hand use and did not account for vocational or recreational hand use. Even with these caveats, the occupational association with CTS was quite tenuous.

I also take issue with the suggestion in the Editorial by Drs Franzblau and Werner³ regarding alternative tools for the diagnosis of CTS. Magnetic resonance imaging (MRI) has both technical and economic limitations, and the limited data in symptomatic and asymptomatic patients do not support its routine use in the diagnosis of CTS. Similarly, their recommendation for measurement of carpal tunnel pressures lacks sufficient scientific foundation. It is quite likely that increased carpal tunnel pressure is the final common pathway in the development of CTS.⁴ However, any clinician who has experience in using Wick catheter measurements of intracompartmental pressure realizes that this test is fraught with technical difficulties and that obtaining reliable measurements is extremely difficult. It is unclear how the use of 2 additional, unproven methods would increase diagnostic accuracy.

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2. Jablecki CK, Andary MT, So YT, Wilkins DE, Williams FH. Literature review of the usefulness of nerve conduction studies and electromyography for the evaluation of patients with carpal tunnel syndrome. *Muscle Nerve*. 1993;16:1392-1414.

3. Franzblau A, Werner RA. What is carpal tunnel syndrome? *JAMA*. 1999;282:186-187.

4. Werner CO, Elmqvist D, Ohlin P. Pressure and nerve lesion in the carpal tunnel. *Acta Orthop Scand*. 1983;54:312-316.

To the Editor: In the epidemiologic study by Dr Atroshi and colleagues¹ estimating the prevalence of CTS in a general population, the nerve conduction studies may have been performed incorrectly. Nerve conduction testing technique and normal values for this study were those described by Kimura,² who recommended warming of the limbs if the skin temperature is be-

low 34°C. Atroshi et al measured skin temperatures of their subjects, but the subjects' hands were not warmed unless their temperature was less than 30°C. Therefore, the temperature requirements used by Atroshi et al will lead to a higher percentage of false-positive results in all clinical categories in their study, which would explain the high percentage of abnormal results (18.4%) in their nonsymptomatic control subjects.

Distal nerve latency increases and nerve conduction velocity decreases when the hand is cool. Kimura³ noted that latencies of the median and ulnar nerves increase by 0.3 milliseconds per degree on cooling the hand. Other authors⁴ advocate warming the limb if its temperature is less than 32°C. Thirty-three percent of control subjects without a history of neuropathy have limb surface temperatures less than 32°C and require warming prior to nerve conduction testing.⁵

In summary, the flawed data collection does not allow an accurate assessment of the prevalence of CTS in this population. Moreover, this study should not be used to support the role of work-related factors in CTS.

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1. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of carpal tunnel syndrome in a general population. *JAMA*. 1999;282:153-158.
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5. Corwin HM, Kasdan ML. Electrodiagnostic reports of median neuropathy at the wrist. *J Hand Surg [Am]*. 1998;23:55-57.

To the Editor: In their Editorial, Drs Franzblau and Werner¹ have painted a picture of extreme diagnostic confusion surrounding the diagnosis of CTS. As a board certified hand surgeon with 15 years of clinical experience, I find that carpal tunnel syndrome is a straightforward clinical syndrome in most patients. It is not difficult to make the diagnosis in the patient with the classic presentation. The American Society for Surgery of the Hand has published guidelines for the diagnosis and treatment of this condition.² Articles such as the one by Franzblau and Warner can lead one to conclude that there is a great deal of confusion in making the diagnosis of CTS.

Most of the confusion in the diagnosis of CTS arises from economic and social considerations and not from the medical facts involved in CTS. While there are various pathophysiologies to CTS, the majority of cases relate to a simple increase in pressure in the carpal tunnel, which can be explained by mechanical means. I believe the assertion that most patients with CTS should be subjected to compartmental pressures or expensive MRI examinations is ludicrous. We are already wasting too much money obtaining nerve conduction studies and electromyographs on many patients who simply do not require those tests, which frequently add nothing to the diagnosis but cost.

Carpal tunnel syndrome remains a discrete clinical entity, which in most patients can be diagnosed without confusion. Conservative treatment and operative treatment when appropriate are effective and yield excellent results in more than 90% of patients.² This result is better than many outcomes in medicine. Most surgeons would rank carpal tunnel surgery as one of their top 5 procedures in terms of patient satisfaction and efficacy.

A textbook dedicated to the subject of CTS has pointed out that "there is no absolute clinical standard or definitive test for CTS."³ Fortunately, a clinical history and a careful physical examination can diagnose this common and highly treatable condition in the vast majority of patients to their benefit.

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1. Franzblau A, Werner RA. What is carpal tunnel syndrome? *JAMA*. 1999;282: 186-187.
2. *The American Society for Surgery of the Hand Clinical Guidelines on CTS*. Chicago, Ill: American Society for Surgery of the Hand; 1996.
3. Rosenbaum RB, Ochoa DI. *Carpal Tunnel Syndrome and Other Disorders of the Median Nerve*. Woburn, Mass: Butterworth-Heinemann; 1993:35.

To the Editor: Several factors cause biases in the CTS prevalence estimates reported by Dr Atroshi and colleagues¹ (at least 1 upward and multiple downward biases); consequently, the accuracy of these estimates is questionable.

The authors used a median-ulnar sensory latency difference of 0.8 milliseconds or longer derived from normal values reported by Kimura² as their electrophysiological criterion of abnormality. However, the practice parameter for electrodiagnostic studies³ cited by the authors in their choice of criterion requires that reference values be obtained with either concomitant studies of a reference population or with previous studies of a reference population in the same laboratory. The Kimura data used by the authors were obtained from a different population in a different laboratory. In fact, Atroshi et al did study an appropriate reference population, that is, asymptomatic respondents to their survey. However, instead of using this reference population to derive the criterion of abnormality to be applied to their test subjects, they applied the Kimura criterion to the asymptomatic responders, yielding an 18.4% rate of supposed subclinical median neuropathy. If the authors had instead appropriately derived their criterion of abnormality from this reference population, their criterion of abnormality would have been significantly higher, yielding lower estimates for the prevalence of CTS. (A criterion of abnormality applied to the reference population from which it was derived is expected to yield 2.5% "abnormal" results for normally distributed populations.)

In addition, several factors may cause the reported prevalence estimates to be biased downward. Most electromyography technicians use several complementary tests of median nerve function in their assessment. A standard practice parameter suggests using 3 tests.³ If the result of any of these tests is abnormal, then the patient is considered to have electromyographically confirmed CTS. Thus, the authors' use of a single

test criterion for each subject would yield lower numbers of abnormal results and lower prevalence estimates compared with the “true” prevalence. At least 10 distinct tests from which to choose are described in another standard text.⁴ Furthermore, by testing sensory function alone, those CTS cases in which only motor nerve fibers are affected would be missed. Finally, by using the median-ulnar comparison alone, rather than, for example, using a median-radial comparison, patients with simultaneous median and ulnar nerve involvement would be missed. A case series of patients with CTS showed that 39% had associated ulnar nerve lesions.⁵

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1. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of carpal tunnel syndrome in a general population. *JAMA*. 1999;282:153-158.
2. Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice*. Philadelphia, Pa: FA Davis Co Publishers; 1989:108.
3. American Academy of Neurology, American Association of Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. Practice parameter for electrodiagnostic studies in CTS [summary statement]. *Neurology*. 1993;43:2404-2405.
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5. Sedal L, McLeod JG, Walsh JC. Ulnar nerve lesions associated with CTS. *J Neurol Neurosurg Psychiatry*. 1973;36:118-123.

In Reply: As Dr Cosgrove notes, persons with bilateral symptoms were diagnosed with clinically certain CTS if the diagnosis was made in 1 or both hands. Similarly, the diagnosis of median neuropathy was made if the nerve conduction testing result was abnormal in 1 or both hands. The diagnosis of clinically and electrophysiologically confirmed CTS required clinically certain CTS and median neuropathy in the same hand. The diagnosis of clinically certain CTS was not based entirely on the presence or absence of physical findings; the history (ie, symptom characteristics) was also important.

Dr Corwin correctly states that both median and ulnar latencies are inversely related to limb temperature. We used the median-ulnar sensory latency difference as the electrophysiological criterion for diagnosing median neuropathy, which should control for temperature. Furthermore, none of the control subjects with abnormal test results had a hand temperature below 32°C and only 4 had a temperature below 33°C (in 2 of these, the latency difference was several milliseconds above the cutoff value). Hand temperature was higher than 32°C in most of the symptomatic subjects with median neuropathy. No correlation was found between hand temperature and median-ulnar latency difference, nor was there any association between the diagnosis (median neuropathy vs no median neuropathy) and hand temperature regardless of temperature limit (below vs $\geq 32^\circ\text{C}$, 33°C , or 34°C , respectively). The temperature limit had no influence on the electrophysiological criterion used for diagnosing median neuropathy, and thus had no influence on the results and conclusions.

When choosing the optimal cutoff value for any “imperfect” diagnostic test, the sensitivity and specificity levels have to be carefully considered in relation to the purpose of the

test. Our cutoff value yielded a sensitivity of 70% (based on the clinical diagnosis) and a specificity of 82%. Similar sensitivity levels for electrodiagnostic tests have been reported in many clinical studies, as shown in the literature review of the American Association of Electrodiagnostic Medicine we cited. The specificity was certainly lower than many have believed or wished. If a higher cutoff value were used, as suggested by Dr Zucker, the sensitivity would have become too low for the diagnostic test to be useful; this does not mean that the true prevalence of CTS is lower than that we reported. We cited other large studies showing similar levels of false-positive results in randomly selected control subjects. It is reasonable to expect current nerve conduction tests to have these levels of sensitivity and specificity in population-based studies. Many electrodiagnostic tests have been described for CTS, with different investigators advocating different tests and arguing for their superiority. When we examined multiple median nerve tests (eg, wrist-palm sensory conduction velocity, distal motor latency, and wrist-digit sensory amplitude) using the laboratory’s normal values, the results did not differ substantially from those reported in our article. Using median-ulnar latency difference could result in missing cases of CTS when there is also ulnar nerve compression at the wrist. However, based on current literature and clinical experience, we do not believe these cases are common.

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In Reply: Both Dr Cosgrove and Dr Stark appear to have misread our position with respect to MRI and intracarpal canal pressures (ICCPs). We do not advocate use of MRI or measurement of ICCP in the routine clinical evaluation of CTS at this time. We believe that MRI and ICCP are 2 test procedures (and there may be others) that deserve further scientific and clinical assessment to determine if they may enhance our ability to more accurately diagnosis CTS, particularly in cases that are not classic or are being considered for surgery. We believe that many patients with CTS, if not the majority, do not present in a classic manner; that is why tests such as nerve conduction studies have assumed such importance. Unfortunately, the interpretation of nerve conduction studies is not necessarily as straightforward as is commonly assumed, which was one of the main points of our Editorial.

Stark also stated, “carpal tunnel syndrome is a straightforward clinical syndrome in most patients. It is not difficult to make the diagnosis in the patient with the classic presentation” Although these statements may be true in his clinic or other referral centers where patients have undergone a multiple-state selection process, Stark’s assertions do not necessarily represent patients presenting to primary care physicians and certainly do not pertain to a general population survey. We agree with his second assertion: making the diagnosis of CTS in a patient with a classic presentation is not difficult. However, the diagnosis is less straightforward when the his-

tory and symptoms are not classic, when the physical examination findings are equivocal, or when the electrodiagnostic studies are borderline. As we have shown in a recent study, only a small fraction of the population complaining of hand or finger symptoms has classic CTS symptoms, positive physical findings, and abnormal electrodiagnostic test results.¹ Most symptomatic people, even those with fairly classic symptoms, do not have positive physical examination findings, abnormal electrodiagnostic test results, or both.¹ The converse is also true: most people with abnormal electrodiagnostic test results do not have classic symptoms of CTS (or any symptoms).¹ As we stated in our Editorial, while nerve conduction studies should be considered an important adjunct in the clinical assessment of CTS, practitioners need to recognize the limitations of the currently available diagnostic tools.

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1. Homan MM, Franzblau A, Werner RA, Albers JW, Armstrong TJ, Bromberg MB. Agreement between symptom surveys, physical examination findings and electrodiagnostic testing for carpal tunnel syndrome. *Scand J Work Environ Health*. 1999;25:115-124.

Ventilator-Induced Lung Injury

To the Editor: Dr Ranieri and colleagues¹ demonstrated that among patients affected by acute respiratory distress syndrome (ARDS), those receiving mechanical ventilation with conventional ventilation showed significantly higher levels of pulmonary and systemic mediators compared with patients who received ventilation with a “lung-protective” strategy. The authors concluded that “mechanical ventilation can induce a cytokine response that may be attenuated by a strategy to minimize overdistension and recruitment/derecruitment of the lung.” The data suggest that ventilator-induced lung injury also can result in systemic inflammation and associated multiple organ failure.

However, I have several concerns about the study’s methods. The authors reported that 7 patients dropped out; these patients were not included in the follow-up. Simply ignoring all patients that withdraw from a clinical trial will bias the results, usually in favor of the intervention. It should be standard practice to analyze the results of clinical trials on an intent-to-treat basis.² The authors also reported the results in terms of mean (SD), without describing the absolute number of patients with increases in levels of each mediator in each group. It is difficult to extract these numbers from the figures in the article. This way of presenting the results does not allow the reader to compute the risk of outcome event in both groups and it does not describe the clinical impact of the lung-protective strategy in terms of “lungs saved from biotrauma,” which remains a surrogate end point.³ Finally, the authors reported only *P* values and did not provide confidence intervals. Thus, it cannot be established how

precise the estimate of the treatment effect was and how likely the results are to be replicable.⁴

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1. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999;282:54-61.
2. Stewart LA, Parmar MK. Bias in the analysis and reporting of randomized controlled trials. *Int J Health Technol Assess*. 1996;12:264-275.
3. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA*. 1996;276:637-639.
4. Guyatt G, Jaeschke R, Heddle N, Cook D, Shannon H, Walter S. Basic statistics for clinicians, II: interpreting study results: confidence intervals. *CMAJ*. 1995;152:169-173.

In Reply: The primary end points of our study were bronchoalveolar lavage (BAL) and plasma concentrations of a number of inflammatory mediators associated with 2 different ventilatory strategies. For safety reasons, we identified a priori criteria to discontinue patients from the study. Seven patients were thus excluded from the study, and we did not obtain cytokine levels at 24 or 36 hours for them. The reasons for the dropouts were documented in our article. Including the patients who dropped out, mortality at 28 days after admission was 59% and 36% and mean (SD) ventilator-free days were 4 (8) days and 12 (11) days in the control and lung-protective treatment groups, respectively. These values are similar to those reported in our article.

Each data point was presented in the original published figures. “Lungs saved from biotrauma” was not a clinical end point in our study; rather, our trial was a “proof-of-concept” study to determine whether ventilatory strategy could impact BAL and serum cytokine levels in humans. As such, the second and third issues raised by Dr Petrucci are more appropriate for a trial for which primary end points are clinically relevant. Such data have recently been obtained in a number of clinical trials¹⁻³ and the recently announced National Institutes of Health ARDS Network, which demonstrated a greater than 20% decrease in mortality in patients receiving a tidal volume of 6 mL/kg compared with 12 mL/kg.^{4,5} Our study suggests a reasonable mechanism⁶ to explain these dramatic results.

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1. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338:347-354.
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Computed Tomography for Predicting Complications of Lumbar Puncture

To the Editor: Dr Attia and colleagues¹ concluded that in the presence of the sensitive clinical signs in adults with possible meningitis, the physician should proceed directly with lumbar puncture (LP) in high-risk patients. Although we agree with this statement we would like to emphasize that lethal complications, such as cerebral herniation, may be caused by LP.² An axial computed tomographic (CT) scan of the head must be obtained to identify those patients at risk. The American Academy of Neurology² indicated that CT is better than clinical examination in predicting the risk of herniation and death in those patients with increased intracranial pressure due to a mass lesion or obstruction of the ventricular system. It has been shown that clinical examination and presence of papilledema are not adequate to exclude the possibility of cerebral herniation.³ Structural characteristics defined by CT provide valuable information about the pressure gradient between different compartments of the brain.

Patients with meningitis have greater risk of harboring mass lesions. Midline shift, loss of suprachiasmatic and basilar cisterns, obliteration of the fourth ventricles, or obliteration of the superior cerebellar and quadrigeminal cisterns with sparing of the ambient cisterns are ominous signs and LP should be avoided.⁴ Although LP is usually a safe procedure, there is enough risk to warrant careful evaluation of these parameters.

The data presented by Attia et al are beneficial for diagnosing adult patients with meningitis. However, clinical suspicion must lead physicians to treat patients empirically and obtain an emergency CT scan of the head before performing an LP.

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1. Attia J, Hatala R, Cook DJ, Wong JG. Does this adult patient have acute meningitis? *JAMA.* 1999;282:175-181.
2. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters: lumbar puncture [summary statement]. *Neurology.* 1993;43:625-627.
3. Korein J, Cravioto H, Leicach M. Reevaluation of lumbar puncture. *Neurology.* 1959;9:290-297.
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In Reply: We appreciate Drs Zaidat and Suarez's caveats regarding CT scanning before LP. The intent of our article was to review the accuracy of the clinical examination in the diag-

nosis of meningitis before other diagnostic tests are undertaken. Once a clinician suspects bacterial meningitis, further testing is warranted provided it does not unduly delay the initiation of appropriate antibiotic treatment.

The risk of LP in adult patients suspected of having meningitis has been debated for years.¹ A systematic review of the retrospective literature on LP in acute meningitis suggests patients at high risk of cerebral herniation may have any of the following clinical features: decreased level of consciousness, focal neurological signs, papilledema, or atypical features (immunocompromised, sinusitis, otitis).¹ In centers with rapid access to CT scanning, the approach suggested by Zaidat and Suarez is appropriate. In centers without access to CT scan technology, LP remains the diagnostic test of choice. Nevertheless, additional prospective studies are necessary to define the incidence of complications following LP in adult patients suspected of having bacterial meningitis and clinical features that may predict which patients are at risk for these complications.

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1. Archer B. Computed tomography before lumbar puncture in acute meningitis: a review of the risks and benefits. *CMAJ.* 1993;148:961-965.

RESEARCH LETTERS

Leprosy in the Eastern United States

To the Editor: While leprosy is known to have been transmitted in Louisiana, Texas, Hawaii, and possibly California, it is not yet endemic in the eastern United States.¹ Exogenous cases of leprosy have been found in the New York City area for some time,² but before 1996 no secondary transmission of leprosy had been documented in this area. Since then, however, we have diagnosed 2 new cases of lepromatous leprosy in people living on the East coast, neither of whom had any obvious history of exposure to this disease.

Report of Cases. The first patient was a 74-year-old woman who had lived her entire life in New Jersey, where she had worked for 17 years as a nurse in an infectious disease unit. Her only overseas travel was a 1-week tour of China, where she stayed in tourist hotels and was not directly exposed to anyone with leprosy. The second patient was a 73-year-old retired chemist who had lived exclusively in New York City and Virginia and had no history of overseas travel. He had had a long history of hypogonadism and hypothyroidism, both of which were likely secondary, in retrospect, to lepromatous leprosy.

Both patients met the following diagnostic criteria: (1) a typical infiltrative skin lesion, (2) positive histology and Fite stains, (3) positive polymerase chain reaction for *Mycobacterium leprae*, and (4) erythema nodosum leprosum that responded to treatment with thalidomide.

Comment. Leprosy, or Hansen disease, is a chronic granulomatous disease. Transmission is thought to require repeated contact with the etiologic *M leprae* organisms. The typical skin lesion is an inflammatory dermatosis that is always without scales, which differentiates it from psoriasis, eczema, and other more common dermatoses. The diagnosis cannot be made without skin biopsy. Because the organisms may not appear with more common acid-fast staining, a Fite stain must be ordered,³ and the pathologist should be made aware of the clinical suspicion of leprosy. Other accompanying signs and symptoms may include peripheral neuropathy, autoimmune endocrinopathy, and arthralgias. Patients may have false-positive antinuclear antibody tests, leading to an incorrect diagnosis of lupus erythematosus. North American clinicians should suspect leprosy in patients who present with these findings, even if they have no obvious risk factors for the disease.

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***Streptococcus equinus* Endocarditis in a Woman With Pulmonary Histiocytosis**

To the Editor: *Streptococcus equinus* is the predominant streptococcus in the alimentary tract of the horse.¹ Although this organism occasionally has been isolated from the human intestine,² to our knowledge it has not been reported to cause endocarditis in patients without prior cardiac disease.

Report of a Case. A 65-year-old woman was referred to us for evaluation of intermittent fever associated with non-productive cough and weight loss. She had not undergone recent dental or invasive procedures, and she had no history of cardiac disease or murmur. The patient's body temperature was 38.2°C; her pulse, 98/min; and her blood pressure, 130/160 mm Hg. A grade 3 early diastolic murmur was audible on the left sternal border and scattered dry crackles were heard on lung auscultation. Ophthalmoscopy and examination of the mouth, ears, nose, throat, abdomen, and nervous system were normal. Laboratory tests showed anemia (hemoglobin, 97 g/L), mild leukocytosis (white blood cell count, $11,000 \times 10^6/L$), and increased erythrocyte sedimentation rate (75 mm/h). Transthoracic and transesophageal echocardiography disclosed the presence of a pedunculated and echodense mass on the posterior leaflet of the aortic valve and a small mass on the anterior leaflet of the mitral valve. Doppler ultrasonography showed severe aortic and mild mitral regurgitation with an ejection fraction of 65%. A honey-

comb pattern was visible on radiographs of the chest with predominance in the middle and upper lung fields. High-resolution computed tomographic scan of the lungs showed multiple bilateral radiolucent areas with diameters from a few millimeters to 5 cm, some with thin walls. The results of pulmonary function studies were normal. Eight out of 8 blood culture bottles were positive for *S equinus*, which was identified with standard microbiologic criteria. Repeated searches for fecal occult blood were negative and the result of a barium enema examination with air contrast medium was normal.

Treatment with piperacillin sodium and gentamicin was begun, and the patient recovered quickly. After 6 weeks of treatment, however, an echocardiogram showed a significant deterioration of left ventricular function, and the patient underwent cardiac surgery with replacement of the aortic valve and mitral valvuloplasty. A biopsy of the lung was performed during surgery. Microscopical examination showed extensive fibrosis of the interstitium with a few Langerhans cells and lymphocytes; cystic spaces with a fibrous wall were present beneath the pleural surface together with focal areas of retraction emphysema. These findings were indicative of an organizing phase of histiocytosis X. The postsurgical course was uneventful and the patient was well 6 months after the operation.

Comment. *S equinus* and *S bovis* are included in the Lancefield group D streptococci. Both *S bovis* and *S equinus* have been isolated from the human bowel in approximately 7% of the general population.² While *S bovis* bacteremia is frequently associated with carcinoma of the colon, *S equinus* only rarely has been described as a human pathogen. The only case of *S equinus* endocarditis reported in the literature occurred in a farmer.³ To our knowledge, ours is the first reported case of the occurrence of *S equinus* endocarditis in a patient who had no preexisting heart disease or evidence of gastrointestinal disease. This patient also had underlying pulmonary histiocytosis X. Many abnormalities of the immune system have been described in patients with this disease, including decreased production of natural antibodies and IgM,⁴ and changes in T lymphocyte phenotype.⁵ These abnormalities can predispose patients with histiocytosis X to bacterial infections,⁶ and a similar mechanism might have occurred in our patient.

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A Prescription Drug Packaged in China and Sold as an Ethnic Remedy

To the Editor: A 30-year-old Chinese-American woman presented to the University of Colorado Allergy and Immunology Clinic with acute urticaria. As there was no clear precipitating event, hydroxyzine was prescribed, and she was advised to call if the medication was inadequate or if the urticaria persisted. Several weeks later, she called to report that the hydroxyzine had worked but it lasted only a short time whereas a “Chinese” medicine purchased over the counter at a local Chinese pharmacy had “lasted much longer.”

The frequent use of unconventional therapies by patients seen by allopathic physicians is well documented,¹ so it was not surprising that this patient had taken an alternative medication. She was asked to bring a sample of this product (which was presumed to be a formulation of Chinese herbs) to her next visit. As shown in the accompanying photograph (FIGURE), the patient’s “Chinese” medicine turned out to be a standard preparation of astemizole clearly labeled in English but packaged for distribution in Asia.

Astemizole is a nonsedating H₁ antihistamine with a half-life of 7 to 19 days. There are significant concerns about cardiotoxicity due to overdose or to inhibition of astemizole metabolism by other drugs that use the P450 pathway, such as ketoconazole and erythromycin.²

The sale of restricted and/or toxic drugs or materials under the guise of “ethnic” cures has a long history. This practice falls into 2 categories: (1) purposeful misrepresentation and (2) sale of pharmaceuticals that require prescriptions in the United States but not in other countries.

One well-known example of misrepresentation was the “Mexican Asthma Cure,” which contained triamcinolone. It was claimed that this preparation was free of adverse effects and did not contain corticosteroids.³ In a recent study,⁴ 32% of Asian patent medicines collected from California retail herbal stores were found to contain undeclared pharmaceuticals or heavy metals.

The practice of selling prescription drugs by ethnic pharmacies has not been well documented in the medical literature. These materials are commonly available over the counter in some countries, are surreptitiously brought into the United States, and sold “under the counter” by pharmacies serving ethnic markets. A prescription may not be required. The extent of this practice is unknown but drugs distributed in this fashion likely include antibiotics, analgesics, and anti-inflammatory drugs, since these drugs are widely available over the counter in many countries.

Figure. Chinese “herbal” preparation containing astemizole



The package of astemizole purchased by this patient is an example of this practice.

Physicians should be aware that medications obtained at an ethnic pharmacy may be bona fide herbal extracts, may be potent pharmaceuticals packaged to resemble herbal extracts, may be herbal extracts adulterated purposely with pharmaceuticals or unintentionally containing heavy metals, or may not be herbal extracts at all. In the case of the patient reported herein, the medicine was clearly a potent pharmaceutical agent with predictable adverse effects and was misunderstood by this patient to be a traditional “Chinese” medicine.

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CORRECTION

Incorrect Wording: In the Letter to the Editor entitled “Clinical Diagnosis of Carpal Tunnel Syndrome” published in the February 23, 2000, issue of THE JOURNAL (2000;283:1000-1003), there was incorrect wording in one of the letters. On page 1001, in the third paragraph of Dr Zucker’s letter, the second and third sentences should read as follows: Most electromyographers use several complementary tests of median nerve function in their assessment. The practice parameter suggests using 3 tests.

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RESEARCH LETTER

Underreporting of Hemorrhagic Stroke Associated With Phenylpropanolamine

To the Editor: Although passive surveillance systems for adverse drug event reporting are often used to detect rare, serious adverse reactions for marketed drugs, they are limited by underreporting. The extent of underreporting is unknown and may be influenced by the severity of the event, the specialty of the reporter, how long the drug has been on the market, whether the event is labeled, and whether the drug is prescription or nonprescription.¹ We attempted to assess the degree of underreporting of hemorrhagic stroke associated with phenylpropanolamine, a nonprescription drug.

Methods. We compared the number of cases of hemorrhagic stroke associated with phenylpropanolamine detected in the Hemorrhagic Stroke Project² with those reported during the same period to the Adverse Event Reporting System of the US Food and Drug Administration (FDA). The Hemorrhagic Stroke Project study was conducted between December 1994 and July 1999 in Connecticut, Massachusetts, Ohio, Kentucky, Rhode Island, and Texas. In an effort to recruit all research subjects who were 18 to 49 years of age and in the areas under study and who had had a hemorrhagic stroke, the Hemorrhagic Stroke Project developed an active surveillance program for hemorrhagic stroke in selected hospitals of the participating states.

Results. In the 5-year period under study, the Hemorrhagic Stroke Project enrolled 702 participants who had had hemorrhagic stroke and were in the target age group, 27 of whom

had been exposed to phenylpropanolamine. During the same period, no states or hospitals in the study area reported cases to the Adverse Event Reporting System. The reporting rate was thus 0% (95% confidence interval, 0%-10.5%).

Comment. This very low rate of passive reporting is consistent with previous estimates. Scott et al³ estimated that less than 1% of suspected serious adverse reactions were reported to the FDA in the 1980s. Rogers et al¹ found that physicians reported only 8% to 13% of serious or life-threatening adverse reactions. We were unable to identify any prior studies of underreporting of a serious adverse reaction caused by a nonprescription drug in the United States.

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1. Rogers AS, Israel E, Smith CR. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Arch Intern Med.* 1988;148:1589-1592.
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CORRECTIONS

Incorrect Wording: A wording error occurred in the Original Contribution entitled "Association Between the T29→C Polymorphism in the Transforming Growth Factor β 1 Gene and Breast Cancer Among Elderly White Women: The Study of Osteoporotic Fractures" published in the June 13, 2001, issue of THE JOURNAL (2001; 285:2859-2863). On page 2860, the last part of the second to the last sentence in "Genotyping Methods" should read: "... followed by a denaturation period of 15 seconds at 95°C for 45 cycles."

Notice of Triplicate Publication: The Research Letter, "Streptococcus Equinus Endocarditis in a Woman With Pulmonary Histiocytosis," by L. A. Sechi, MD, and R. Ciani, MD, published in the February 23, 2000, issue of THE JOURNAL,¹ is virtually identical to a case report by the same authors published in the *Scandinavian Journal of Infectious Diseases*, 1999² and to a letter to the editor by the same authors published in *The American Journal of Medicine*, 2000.³

The author had sent a signed statement of authorship responsibility to the editors of THE JOURNAL stating that their manuscript had not been published and was not under consideration for publication elsewhere. They also signed a document that transferred all copyright ownership to the publisher. Well before publication, Drs Sechi and Ciani received a letter of acceptance from THE JOURNAL reminding them of our policy on duplicate publication.

1. Sechi L, Ciani R. *Streptococcus equinus* endocarditis in a woman with pulmonary histiocytosis. *JAMA.* 2000;283:1005.
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