

Correspondence



A Poliomyelitis-like Syndrome from West Nile Virus Infection

To the Editor: Muscle weakness is a common finding and an important predictor of death in patients with West Nile virus encephalitis.^{1,2} Yet this important sign does not have a defined pathological basis. In monkeys, horses, and birds, West Nile virus causes poliomyelitis.³⁻⁵ Our clinical and electrodiagnostic findings in three consecutive patients with

confirmed West Nile virus infection suggest that the virus also attacks the spinal cord in humans.

Patient 1, a 56-year-old man, presented with fever, chills, night sweats, myalgias, and confusion. Weakness gradually developed in his arms, along with flaccid paralysis in his right leg, areflexia, bladder dysfunction, and acute respiratory distress. He reported that he had no pain or paresthesias. Sensory examination was normal. Suspected diagnoses included stroke, Guillain-Barré syndrome, and inflammatory myopathy, for which he received anticoagulation therapy and intravenous immune globulin and underwent muscle biopsy. Cerebrospinal fluid showed 3 white cells per cubic millimeter, a glucose level of 54 mg per deciliter, and a protein level of 89 mg per deciliter. Magnetic resonance imaging (MRI) of the brain and cervical spine was normal. In an enzyme-linked immunosorbent assay, the ratio of IgM antibodies against West Nile virus (the ratio of the reactivity of the patient's serum to West Nile virus antigen to the reactivity of

TABLE 1. MOTOR AND SENSORY AMPLITUDES.*

NERVE	STIMULATION SITE	RECORDING SITE	PATIENT 1		PATIENT 2		PATIENT 3		NORMAL VALUES
			RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	
Median motor nerve (mV)	Wrist	Abductor pollicis brevis	3.9	—	3.8	—	2.0	11.4	≥5.0
Median sensory nerve (μV)	Wrist	Second digit	20.4	—	34.4	—	33.4	35.4	≥20.0
Ulnar motor nerve (mV)	Wrist	Abductor digiti minimi	5.0	—	4.4	—	1.6	7.5	≥4.5
Ulnar sensory nerve (μV)	Wrist	Fifth digit	18.8	—	17.8	—	28.8	27.6	≥15.0
Musculocutaneous motor nerve (mV)	Erb's point	Biceps	2.4	—	—	—	0.2	7.6	≥4.0
Musculocutaneous sensory nerve (μV)	Elbow	Forearm	10.6	—	17.2	—	27.1	32.6	≥10.0
Axillary motor nerve (mV)	Erb's point	Deltoid	1.7	—	0.3	—	0.4	5.3	≥4.0
Radial sensory nerve (μV)	Forearm	Dorsum of hand	23.2	—	48.6	—	31.9	31.8	≥15.0
Peroneal motor nerve (mV)	Ankle	Extensor digitorum brevis	NR	4.2	1.2	0.1	—	—	≥2.0
	Knee	Tibialis anterior	0.2	2.8	—	0.4	—	—	≥4.0
Peroneal sensory nerve (μV)	Leg	Dorsum of foot	2.2	3.1	6.6	7.1	—	—	≥5.0
Tibial motor nerve (mV)	Ankle	Abductor hallucis	2.5	7.6	2.8	3.3	—	—	≥3.0
Sural sensory nerve (μV)	Posterior leg	Ankle	8.4	9.7	13.3	14.8	—	—	≥8.0

*NR denotes no response.

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control serum to the same antigen) was 14.78:1 (reference ratio, <2.00:1). Electrodiagnostic studies showed reduced motor responses, preserved sensory responses, and scattered denervation without evidence of myopathy or polyneuropathy (Table 1).

Patient 2, a 57-year-old man, presented with fever, chills, nausea, vomiting, and headache. Asymmetric flaccid paralysis developed, involving the distal portion of the left leg, the right thigh, and the right arm, as well as areflexia, dysphagia, urinary incontinence, and acute respiratory distress requiring mechanical ventilation. The patient reported having no altered sensation. Sensory examination was normal except that there was a slight decrease in vibratory sensation in the toes bilaterally. Cerebrospinal fluid showed 80 white cells per cubic millimeter, a glucose level of 99 mg per deciliter, and a protein level of 196 mg per deciliter. The virus-specific IgM ratio was 24.48:1. MRI of the brain was normal. Electrodiagnostic studies showed reduced motor responses, normal sensory responses, widespread denervation, and neurogenic recruitment (Table 1).

Patient 3, a 50-year-old man, presented with severe nausea, vomiting, headache, and diarrhea, but no fever. He was given a diagnosis of food poisoning, but flaccid paralysis developed, together with areflexia limited to the right arm, without pain or paresthesias. Sensory examination was normal. He received anticoagulation therapy for suspected stroke, although MRI of the brain was normal. The ratio of IgM against West Nile virus was 2.08:1. No spinal tap was performed. After the patient was transferred to a rehabilitation hospital, the IgM ratio was 25.74:1. Electrodiagnostic studies showed markedly reduced motor responses in the monoplegic limb, with normal sensory responses (Table 1).

Asymmetric flaccid paralysis and areflexia developed in all three patients, and two had bladder dysfunction and acute respiratory distress. Electrodiagnostic findings confirmed involvement of anterior horn cells or motor axons. These clinical and electrodiagnostic findings are classic features of poliomyelitis and strongly suggest that in humans, as in animals,³⁻⁵ the spinal cord gray matter is a target of West Nile virus. The poliomyelitis-like presentation in our cases warrants a reevaluation of other cases of West Nile virus with similar presentation that have previously been attributed to Guillain-Barré syndrome or axonal polyneuropathy.^{1,2} Awareness that muscle weakness with West Nile virus infection may be of spinal origin should help to eliminate misdiagnoses and inappropriate treatment, and it should encourage pathological study of the spinal cord.

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This letter was published at www.nejm.org on September 23, 2002.

Poliomyelitis Due to West Nile Virus

To the Editor: Poliomyelitis is a clinical syndrome defined by the presence of fever, meningitis, and flaccid paralysis. In the United States, this syndrome was historically associated with infection by poliovirus but is now more commonly seen with other enteroviruses. We describe a case of poliomyelitis in a patient infected with West Nile virus, a flavivirus.

A 50-year-old woman from Louisiana had a headache on the day before she traveled to Georgia for the July 4 holiday. After she arrived, her headache worsened, and she had severe myalgia. Two days after the onset of headache, weakness developed, and the patient was admitted to the hospital. She was febrile (temperature, 39.5°C) but was awake, alert, and fully cognizant. She had moderate bifacial and appendicular weakness (Medical Research Council grade 4-5), with a normal sensory examination and retained deep-tendon reflexes. Lumbar puncture showed 54 white cells per cubic millimeter (22 percent neutrophils), with a normal glucose level and a protein level of 110 mg per deciliter (normal level, <45 mg per deciliter).

She remained febrile through the eighth day. Her weakness progressed, and she required intubation on the sixth day after the onset of headache, when she could no longer lift her head or move her arms or legs against gravity. Her cognition, sensation, and reflexes remained normal. Magnetic resonance images of the complete spinal cord were normal. Serial electrodiagnostic findings are presented in Table 1.

On day 12 of hospitalization, a cerebrospinal fluid specimen tested positive for antibodies against West Nile virus (IgM titer, 1:256; IgG titer, 1:128). Stool cultures and polymerase-chain-reaction studies for the presence of enteroviruses were negative. Two months after the onset of weakness, the patient remains in a rehabilitation facility and requires respiratory assistance.

TABLE 1. ELECTRODIAGNOSTIC DATA.

VARIABLE	DAY 4	DAY 11	DAY 18
Sensory amplitudes	Normal	Normal	Normal
Motor amplitudes	Normal	25-50% of normal	25-50% of normal
Motor distal latencies	Normal	Normal	Normal
Conduction velocities	Normal	Normal	Normal
Spontaneous activity on electromyography	None	None	Profuse in proximal and distal muscles
Motor units and recruitment	Patient sedated	Normal motor units, severely reduced recruitment	Normal motor units, severely reduced recruitment

This unusual clinical presentation of paralytic poliomyelitis is distinguished from Guillain-Barré syndrome, the most common cause of acute flaccid paralysis in the United States, by the presence of fever, pleocytosis, and retained tendon reflexes. Electrodiagnostic studies during the acute phase of the illness confirmed the pure motor nature of her illness, excluded demyelination as a pathogenic mechanism, and identified the anterior horn cell as the site of pathology.

Previous reports of West Nile virus, including those from the New York City outbreak of 1999, described patients with weakness.^{1,2} The mechanism underlying weakness in West Nile virus has not been clearly established, and in some cases, this symptom has been attributed to Guillain-Barré syndrome. Our data and those of previous studies are consistent with effects at the level of the anterior horn cell. Autopsies in four patients did not include spinal cord.³

Poliovirus attacks motor neurons by attaching to the poliovirus receptor on the anterior horn cell. Flaviviruses other than West Nile virus are not known to cause poliomyelitis. These findings raise the possibility that these viruses can attack motor neurons directly.

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This letter was published at www.nejm.org on September 23, 2002.

Tissue Plasminogen Activator in Cardiac Arrest with Pulseless Electrical Activity

To the Editor: In contrast to previous trials,^{1,2} the study reported by Abu-Laban et al. (May 16 issue)³ showed no beneficial effects of fibrinolysis in patients with cardiac arrest and pulseless electrical activity. However, Abu-Laban et al. studied a subgroup with an exceptionally poor prognosis.⁴ We are not aware of other studies in which there were no survivors in the placebo group. Even therapeutic strategies with proven efficacy in patients with cardiac arrest, such as hypothermia,⁵ would have failed in this study population. To test validly for efficacy, it is important to study populations that might also survive without specific treatment. Moreover, treatment with tissue plasminogen activator (t-PA) was initiated a mean of 36 minutes after the patient's collapse, by which time ineffective resuscitation procedures have mostly been terminated. Nevertheless, the group size was calculated on the assumption that treatment would change the rate of survival to hospital discharge from 1.0 percent (in the placebo group) to 10.3 percent (in the t-PA group) — an increase of 930 percent. Such prerequisites

might a priori preclude the demonstration of any positive effect of an intervention.

In contrast to previous studies,¹ the administration of heparin was not mandatory. Nevertheless, 5 of 13 patients (38 percent) who were admitted received heparin, which may suggest an additional beneficial effect. Therefore, the number of patients per group who received this medication should be clarified.

For conclusive investigation of the effects of t-PA in cardiac arrest, t-PA must be given early to patients with a better prognosis, such as those with a witnessed arrest, ventricular fibrillation, or both. Such a study is currently under way in Europe, and when the results are available, the controversy over fibrinolysis in cardiac arrest can be resolved.

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To the Editor: Fibrinolytic, antiplatelet, and antithrombotic agents are promising for the treatment of cardiac arrest. Cardiopulmonary resuscitation (CPR) can alter the pharmacokinetics of these agents, making higher dosages or bolus administration necessary. Laboratory studies must therefore precede clinical trials. We have previously noted that the grave nature of cardiac arrest may explain the tendency to rush into clinical trials, but it may not justify the potential harm from false negative findings.¹

Concern about the administration of a potentially harmful agent under "implied consent" may not be mitigated by using it late, when it may be ineffective. In this study, fibrinolysis may not have been achieved before irreversible injury occurred.

Perfusion pressure during CPR is the difference between arterial and venous pressures.² The administration of 500 ml of intravenous saline is not standard practice and may decrease perfusion. Bicarbonate is additional volume, and lidocaine's sodium-channel blockade may cause asystole³ — neither agent is part of standard therapy.

Because fewer patients who underwent autopsy had pul-

monary embolism or acute myocardial infarction than in other series,⁴ less than one quarter may have been susceptible to a benefit. The inclusion of patients with initial asystole also reduced the proportion with a potential response. This study population may not have been optimal, since other medical systems have had better results with pulseless electrical activity.⁵ We refer to this as a “graveyard effect”; a better term might be “rancid sample,” as proposed by the late epidemiologist Dr. Alvan Feinstein. This study does not “exclude” an increase in survival, because when the control outcome is zero, the efficacy remains unknown.

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The authors reply:

To the Editor: We disagree with the suggestion that our study was predestined to have negative results. Böttiger et al. state that t-PA must be evaluated in patients with a witnessed arrest, initial ventricular fibrillation, or both. Sixty-six percent of our study population met this requirement. Paradis et al. question research on subgroups with poor outcomes; however, it has not been established that a high base-line survival rate is required to assess the management of pulseless electrical activity validly. We specifically studied this rhythm because of its association with pulmonary embolism¹ and the documented potential for forward blood flow and good outcomes despite prolonged pulselessness. Most reports on fibrinolysis involve cases in which patients have pulseless electrical activity and are expected to die, yet a review of 67 such cases showed a 75 percent survival rate and a mean duration of arrest of 51 minutes.² Our sample-size requirement was based on these reports and a more modest survival rate of 30 percent for the targeted subgroup.

We anticipated that 1 percent of eligible patients would survive; thus, the outcome in our placebo group was not surprising. Of 467 ineligible patients with pulseless electrical activity, 4.7 percent survived. Most such survivors have an early response to the initial therapies that we thought

would have been inappropriate to omit before the administration of t-PA. Intravenous saline is considered standard therapy for pulseless electrical activity by the British Columbia Ambulance Service. The influence of fluids on perfusion pressure, with the various causes of pulseless electrical activity, remains poorly understood. Neither bicarbonate nor lidocaine was mandated by our protocol, and the proportions of patients who received these agents reflect local practice.

We believe our time intervals represent the reality of out-of-hospital administration of a reconstituted fibrinolytic agent after a rapid trial of initial therapies. On the basis of numerous reports, these intervals would not negate the possibility of a response. Unfortunately, the studies with positive results are methodologically weak and provide no data on timing,^{3,4} precluding a comparison with our trial. In response to the question about heparin, of the five patients who were given heparin, three received t-PA.

We agree that laboratory studies are helpful but certainly do not believe we rushed into a clinical trial. Our study arose logically from a foundation of numerous reports involving humans, as did two recent articles calling for clinical trials of fibrinolytic agents in cardiac arrest.^{2,5} In our article, we candidly discuss the limitations of our study, many of which the correspondents repeat, and note that our results do not exclude the possibility of a role for fibrinolytic therapy. Although we stand by our conclusions, we look forward to the results of the European trial and other trials.

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Salmeterol for the Prevention of High-Altitude Pulmonary Edema

To the Editor: Sartori and colleagues (May 23 issue)¹ demonstrate the marked benefits of salmeterol in the secondary prevention of high-altitude pulmonary edema. The authors propose that this benefit occurs through changes in pulmonary transepithelial sodium transport rather than hemodynamic effects, because salmeterol did not alter the heart rate or peak pulmonary pressures.

However, the authors did not assess the nasal transepithelial potential difference at high altitude, nor did they

determine the effect of salmeterol administration on this gradient. Furthermore, there was no measurement of mean pulmonary pressure, cardiac output, central filling pressures, or systemic blood pressure. In addition, only a derived peak systolic pulmonary pressure was determined, and this measure may not reflect changes in pulmonary vascular resistance.

We and others have demonstrated that inhaled albuterol is associated with increases in cardiac output and decreases in vascular stiffness without changing the heart rate or systemic blood pressure.^{2,3} Moreover, these effects are associated with increased plasma albuterol concentrations and may be attenuated by a nitric oxide synthase inhibitor.³ It has previously been suggested that nitric oxide has a role in the pathogenesis of high-altitude pulmonary edema. Concentrations of exhaled nitric oxide are reduced by hypoxia,⁴ and inhaled nitric oxide is an effective therapy for high-altitude pulmonary edema.⁵ Although we recognize the difficulties involved in undertaking research at high altitude, we believe that a more detailed assessment is needed before a significant hemodynamic effect of salmeterol in the prevention of high-altitude pulmonary edema can be ruled out.

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To the Editor: Sartori et al. report that inhalation of high-dose salmeterol (three times the normal dose) results in a 50 percent reduction in the incidence of high-altitude pulmonary edema in susceptible persons who ascend rapidly to high altitude. They attribute the beneficial effects to stimulation of sodium reabsorption from the alveoli mediated by β_2 -adrenergic receptors. Unfortunately, salmeterol is not the right drug with which to test this hypothesis. Besides stimulation of sodium reabsorption, salmeterol has several other actions that might better explain the prevention of high-altitude pulmonary edema. These actions include tightening of the alveolar-capillary barrier and lowering pulmonary-artery pressure directly and through mediation by peripheral chemoreceptors, as well as indirectly through hypoxic ventilatory stimulation¹ and increased nitric oxide production. The same authors have shown that Doppler echocardiography, in contrast to invasive measurements, reveals a big overlap of systolic pulmonary-artery pressure between susceptible persons with and without high-altitude pulmo-

nary edema.² Thus, the absence of significantly higher pulmonary-artery pressure with placebo does not rule out the possibility that salmeterol was acting as a vasodilator, particularly during climbing, when pulmonary-artery pressures were highest. A variable time between inhalation and the measurement of pulmonary-artery pressure could be another confounding factor. Finally, our recently published observations³ of high red-cell counts and protein concentrations without signs of inflammation in alveolar-lavage fluid of persons with high-altitude pulmonary edema indicate that the integrity of the alveolar-capillary barrier is disturbed in early stages of the condition. Since intact epithelial-barrier function is crucial for the reabsorption of alveolar fluid in humans,⁴ our findings argue against stimulated fluid reabsorption as the mechanism of prevention of high-altitude pulmonary edema by salmeterol.

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To the Editor: Since the publication of a previous article by Sartori et al.,¹ we have been using albuterol (Ventolin) inhalers or nebulizers in the Himalayas for the treatment of patients with high-altitude pulmonary edema. Our anecdotal experience indicates an increase in the pulse-oximeter reading after the administration of this drug in subjects with high-altitude pulmonary edema. Clearly, a formal study needs to be done. However, the studies by Sartori et al. raise a question about persons who are susceptible to a life-threatening illness such as high-altitude pulmonary edema: why would they reexpose themselves to high altitudes, especially if they were on their own and not participants in a study?

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1. Sartori C, Lipp E, Duplain H, et al. Prevention of high-altitude pulmonary edema by beta-adrenergic stimulation of the alveolar transepithelial sodium transport. *Am J Respir Crit Care Med* 2000;161:A415. abstract.

To the Editor: The recent article on the use of salmeterol for the prevention of high-altitude pulmonary edema omits mention of the incidence of smoking among subjects in the comparison groups. Cigarette smoke is an important source of nitric oxide. Even though pulmonary-artery pres-

tures measured by echocardiography at selected time points showed no significant difference between the groups that were compared, it is known that nitric oxide from cigarette smoke can cause vasodilatation^{1,2} and has been shown to affect amiloride-sensitive sodium channels directly.^{3,4} Therefore, differential rates of cigarette smoking could introduce a bias into such a study and affect the results.

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To the Editor: In his Perspective article,¹ Voelkel proposes that inflammation is a causal factor in high-altitude pulmonary edema. We suggest that recent evidence supports a view that inflammation may not be pathogenetic in high-altitude pulmonary edema. Rather, the condition has a hydrostatic basis with unique fluid characteristics. In catheterization studies, Maggiorini et al.² found that susceptible subjects in whom high-altitude pulmonary edema develops not only have very high pulmonary-artery pressures but are also critically distinguished from those without high-altitude pulmonary edema by microvascular pressures above 20 mm Hg. The stress-induced failure of alveolar capillaries results in a generalized breach of the alveolar-capillary barrier with leakage of erythrocytes and plasma constituents. Bronchoalveolar-lavage studies performed in patients with high-altitude pulmonary edema lasting more than a day^{2,3} have in some cases found high neutrophil counts and inflammatory cytokine concentrations, providing the strongest evidence for the inflammatory theory of causality. In contrast, Swenson et al.³ have very recently shown that there is no evidence of inflammation of the alveolar space in climbers who are susceptible to high-altitude pulmonary edema within 24 hours after their arrival at an altitude of 4559 m (there may be mild alveolar hemorrhage and increased plasma protein levels but there are no increases in neutrophil counts or cytokine concentrations); these findings applied to those with high-altitude pulmonary edema and to those in whom it developed within the next day. Similarly, there were no elevations in the levels of a host of inflammatory cytokines in circulating blood.⁴ Furthermore, harvested alveolar macrophages from these subjects (both at low altitude and at 4559 m) do not release inflammatory or chemotactic cytokines with alveolar hypoxia sufficient to cause high-altitude pulmonary edema.⁵ These data suggest that inflammation

in high-altitude pulmonary edema is a secondary reaction to the initial hydrostatic injury.

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The authors reply:

To the Editor: We found that subjects who are susceptible to high-altitude pulmonary edema had a defect of the respiratory transepithelial sodium transport and that salmeterol, at a dose known to stimulate this transport (and at the upper limit of the dose recommended for the treatment of asthma), decreased the incidence of pulmonary edema in highly susceptible subjects. Drs. Bärtsch and Mairbaurl suggest that alternative mechanisms, also discussed in our article, were responsible for the favorable effects of salmeterol. A few clarifications must be made, however. In studies using vasodilator agents to treat or prevent high-altitude pulmonary edema, the decreases in systolic pulmonary-artery pressure needed to attain this aim were large and were easily detectable by echocardiography.^{1,2} The integrity of the alveolar-capillary barrier is not an absolute condition for the stimulatory effects of β -adrenergic agonists on sodium transport in the lung,³ and the evidence of a disruption of this barrier during the development of high-altitude pulmonary edema is scanty at best. Moreover, salmeterol tightens the alveolar-capillary barrier, which may explain why its stimulatory effect on sodium and water transport is preserved even in the presence of a hypothetical disturbance of the function of the alveolar capillary barrier.

Dr. Cruden and colleagues ask for invasive hemodynamic measurements at high altitude and refer to work using surrogate measurements of cardiac output and systemic arterial stiffness after inhalation of albuterol. Although the relevance of such observations with regard to pulmonary vascular responses to salmeterol at high altitude is not obvious, invasive hemodynamic measurements in subjects susceptible to high-altitude pulmonary edema would certainly be of interest. However, we have some serious concern about whether, for this specific issue, the potential gain in knowledge justifies the risks related to the use of invasive meas-

urements in seriously ill subjects in a high-altitude setting.

Dr. Prodan and colleagues refer to smoking-related inhalation of nitric oxide, an effective treatment for high-altitude pulmonary edema,¹ as a potential confounding variable. None of the subjects smoked.

Dr. Basnyat's observation of a benefit of albuterol inhalation for the treatment of established high-altitude pulmonary edema is very interesting and concurs with similar anecdotal experiences of others. It clearly deserves formal testing. We also agree with his caveat regarding the risks of reexposure to high altitude in subjects susceptible to high-altitude pulmonary edema.

The dispute over the exact underlying mechanism by which salmeterol may cause its favorable effects should not obscure the primary new conclusion of the study for practicing physicians and mountaineers: salmeterol prevents high-altitude pulmonary edema.

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Sirolimus-Eluting Coronary Stents

To the Editor: The results of the RAVEL study (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) (June 6 issue)¹ are promising and bring to light the ethical and financial dilemma that is likely to surface once drug-eluting stents are approved for general use. The projected cost of each stent is likely to be about \$3,200. Of course, from a financial and societal standpoint, it will not be possible to deploy drug-eluting stents in every case of percutaneous coronary-stent intervention. From an individual patient's standpoint, a drug-eluting stent may be a panacea for a given treated lesion. How does one arrive at a balance? In what cases should the use of a drug-eluting stent be considered absolutely justified and maybe even crucial? We need to arrive at guidelines to determine the point at which the cost of the device offsets the need for repeated coronary interventions, especially in situations in which the risk of restenosis is high or in which presentation with restenosis will probably result in coronary-artery bypass surgery. For example, in patients with diabetes who have a long diseased segment in a small-caliber, proximal left anterior descending artery, treatment with a drug-eluting stent may make good sense. However, a focal lesion in a large-caliber, distal right posterolateral branch in a non-

diabetic, nonsmoking patient may not justify the use of a drug-eluting stent.

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Dr. Morice replies:

To the Editor: Sharma and colleagues raise a crucial issue. The cost of drug-eluting stents is indeed very high. However, this high initial cost is expected to be significantly offset by the reduced rate of recurrent events and the subsequent reduced need for repeated intervention observed in our study at one year among the recipients of sirolimus-eluting stents. The cost-effectiveness analysis that was an objective of the RAVEL trial should provide a clearer picture of the financial aspects of the use of these new devices. As they are increasingly used, the price of these stents is likely to decrease, as is often the case with any new device.

In the meantime, the frustration felt by physicians and their patients in view of the financial dilemma rightfully underlined by Sharma et al. seems more than justified. Nevertheless, the spectacular therapeutic progress brought about by the drug-eluting stents is a reality that cannot be denied.

The following RAVEL investigators were inadvertently omitted in the Appendix to our article: C.R. Costantini, M. de Freitas Santos, S.G. Tarbine, D.A. Zanertini, and J.L. Lazarte, Clínica Cardiología C. Costantini, Curitiba Paraná, Brazil.

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Institutional Review Board Reform

To the Editor: A "central institutional review board," as proposed by Christian et al. (May 2 issue),¹ may be a national ethics review board or a central research ethics committee, but it cannot be an institutional review board (IRB). By definition, a central board "at the national level" transcends an institution.

The continued use of the term "institutional review board" may merely be the result of a habit that is hard to break, or it might reflect something deeper. The term does not contain the word "ethics," implicitly elevating the institutional focus over the ethical focus. It also suggests that local IRBs should still have ultimate authority, despite the problems of duplicative reviews, dissipation of resources, delays, lack of experience and expertise, and conflicts of interest that are inherent in institution-based reviews. We should not continue to use inaccurate labels that also send

the wrong message and impede acceptance of a more centralized review process.

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To the Editor: The articles by Steinbrook,¹ Christian et al.,² and Slater³ (May 2 issue) addressed IRB reform as a means of improving the protection of research subjects. On the basis of my experience as chairman of the IRBs at two major academic medical institutions for a total of 18 years, I would argue that serious risk to patients is more likely to be the result of human fallibility than of inadequate IRB procedures. Adequate IRB procedures could not have prevented the deaths of the student at the University of Rochester from an excessive dose of lidocaine, the volunteer at Johns Hopkins from the pulmonary damage inflicted by hexamethonium, the patient at the University of Pennsylvania from a genetically modified agent, or the nurse at Case Western Reserve from an overdose of methionine. These deaths were the result of a variety of human failings. The most zealous overhaul of IRB regulations and the expenditure of substantial sums to enforce them cannot avert the harm that results from unexpected events or is inflicted by an investigator's sociopathy, hubris, or carelessness.

However, I do believe that an increased emphasis on whistle-blower mechanisms can deal more effectively with the potential problems engendered by the character flaws of investigators. Members of the research community, at all levels, should be made aware of their responsibility to report deviations from protocol. Such mechanisms exist to deal with misconduct in science. They should be vigorously applied in medical research.

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To the Editor: Christian and colleagues have provided an informative explication of the operations of a central institutional review board (CIRB) associated with the National Cancer Institute. The authors' statement that the "diverse perspectives and expertise of the board's members have resulted in a rich discussion of issues that is unmatched by many local IRBs" must be supported. I suggest that the board make public its deliberations. This action will permit the members of other IRBs, potential trial participants, and the general public to judge the manner in which the CIRB members evaluate whether the requirements for the ethical conduct of clinical research are met. Other IRBs may subsequently decide to adopt those features of the CIRB's re-

view process that they deem meritorious or to acquire members with an equivalent range of expertise.

Making this material publicly accessible will also set an important precedent with respect to ending the traditional, but unjustified, secrecy surrounding the deliberations of IRBs.¹ It will do so notwithstanding the fact that the minutes of the CIRB will be subject to public disclosure pursuant to an applicable law in the State of Maryland taking effect on October 1, 2002.²

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1. Ashcroft R, Pfeffer N. Ethics behind closed doors: do research ethics committees need secrecy? *BMJ* 2001;322:1294-6.
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To the Editor: The recent efforts detailed by Dr. Steinbrook toward "improving protection for research subjects" should not cause us to forget how the current system treats subjects who are, in fact, injured by virtue of their participation in research. Specifically, we must ensure that persons who suffer research-related injuries do not have to bear the additional indignity of having to pay for such injuries out of their own pockets. Unfortunately, they largely have to do so under the current system. This is ethically indefensible.

We all benefit from medical research. People who become research subjects are exposed to the small but real chance of being injured; we should all pay for these injuries. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report in 1982 calling for a national policy for the compensation of subjects for research-related injuries.¹ This theme was echoed by the Advisory Committee on Human Radiation Experiments.² Despite these efforts, no national policy to protect human subjects from being stuck with a bill for expenses due to research-related injuries has been established. A number of other countries have such policies in place. It is time that the United States followed suit.

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Pleural Effusion

To the Editor: The criteria discussed by Light in his *Clinical Practice* article on pleural effusion (June 20 issue)¹ are stringent and highly sensitive in identifying an exudate.

However, their specificity is low, particularly in patients with heart failure. Studies have shown that up to one third of pleural-fluid specimens from the subgroup of patients with the sole diagnosis of congestive heart failure fulfill at least one of Light's criteria for an exudate.^{2,3} We found that patients with congestive heart failure who had false positive results were more likely to meet only one of Light's criteria and to have received intravenous diuretics within 24 hours before the pleural tap. A possible explanation is that diuretics shift fluids from the pleural space, thereby changing biochemical transudates into exudates.⁴

A careful evaluation of the number of positive criteria and of whether a patient has recently received diuretic treatment could improve the specificity of Light's criteria in patients with congestive heart failure.

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Dr. Light replies:

To the Editor: I agree with Drs. Fridlender and Gotsman that pleural-fluid samples from many patients with congestive heart failure fulfill at least one of Light's criteria for an exudate. I would add that laboratory values for patients with heart failure alone that fulfill Light's criteria for an exudate usually only barely do so. As I mentioned in the article, measuring the difference between the serum and the pleural-fluid albumin levels is useful in such patients since a difference greater than 1.2 g per deciliter is consistent with a transudative effusion, even though other criteria for an exudative effusion have been met.¹

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1. Burgess LJ, Maritz FJ, Taljaard JJ. Comparative analysis of the biochemical parameters used to distinguish between pleural transudates and exudates. *Chest* 1995;107:1604-9.

Cryptosporidiosis

To the Editor: We wish to elaborate on the risks and prevention of nosocomial cryptosporidiosis, briefly discussed in the review of cryptosporidiosis by Chen and colleagues (May 30 issue).¹ Multiple nosocomial outbreaks of cryptosporidiosis have resulted from direct and indirect person-to-person transmission; one outbreak was due to spread of

the parasite from an ice chest contaminated by a patient.² Cryptosporidiosis in adults should be managed with the use of standard precautions; in incontinent or diapered children less than six years of age, it should be managed with contact precautions. This recommendation of the Centers for Disease Control and Prevention was recently validated in a retrospective cohort study of 37 hospitalized patients that failed to identify roommate-to-roommate transmission of cryptosporidia.³

Cryptosporidium parvum has been shown to be resistant to the germicides used for disinfection, including quaternary ammonium compounds, phenolic compounds, 70 percent ethyl alcohol, and 2.4 percent glutaraldehyde.⁴ The absence of outbreaks due to use of gastrointestinal endoscopes probably results from physical removal of the organisms by cleaning and rapid inactivation of *C. parvum* by drying.⁴ Proper cleaning before disinfection is therefore crucial to the prevention of cross-transmission by gastrointestinal endoscopes, since cleaning removes approximately 10,000 organisms.

C. parvum is relatively resistant to chlorine at the levels used in potable water. For this reason, it has been recommended that patients who are infected with the human immunodeficiency virus⁵ and those who have received hematopoietic stem-cell transplants⁶ minimize their risk of acquiring cryptosporidiosis from water by drinking either filtered water or water that has been boiled for at least one minute. It may be prudent for hospitals to provide all immunocompromised persons with sterile water and sterile ice.

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Weight Loss in HIV-Infected Patients

To the Editor: Recent reports have highlighted the risk of hyperlactatemia and multiorgan failure in human im-

munodeficiency virus (HIV)-infected patients receiving interferon plus ribavirin for chronic hepatitis C.^{1,2} The mitochondrial toxicity of nucleoside analogues seems to be associated with these effects. Hyperlactatemia and pancreatitis have also recently been reported in patients taking didanosine and ribavirin.^{2,3} Since *in vitro* studies have shown that the presence of ribavirin reduces the amount of didanosine needed to suppress HIV,³ it is not surprising that potentiation of didanosine by ribavirin may increase its toxicity. Available data seem to confirm that there is a greater risk of pancreatitis when stavudine or didanosine is taken concurrently with therapy for hepatitis C virus (HCV) infection than when other nucleoside analogues are used.⁴

We wondered whether other side effects of nucleoside analogues might also be potentiated by ribavirin. During the course of a trial of interferon plus ribavirin, we noticed a rapid and significant loss of body weight among the HIV-infected subjects initially recruited for the study (up to 9 kg within six months in one patient). Likewise, the patients described by Lefeuvre et al.¹ and others² presented with asthenia, remarkable weight loss, and hyperlactatemia.

To assess whether synergistic toxicity between ribavirin and nucleoside analogues was responsible for the significant weight loss we observed, we analyzed 47 patients coinfecting with HIV and HCV (83 percent male; mean age, 38 years) who completed six months of therapy with interferon (3 million U three times per week) plus ribavirin (400 mg twice daily) while receiving antiretroviral therapy. At base line, their mean CD4 count was 573 per cubic millimeter, and 60 percent had plasma HIV RNA levels below 50 copies per milliliter. Significant weight loss occurred during therapy for HCV (approximately 4 kg, on average) in parallel with elevations in the serum lactate and amylase levels (Table 1). A trend toward an association between higher lactate and amylase levels and more pronounced weight loss was found among patients taking didanosine or stavudine, as compared with those taking other nucleoside analogues. We have not, in our experience, observed comparable weight loss in patients taking interferon plus ribavirin alone or in those taking antiretroviral drugs.

Our observations support the existence of synergistic toxicity, probably mitochondrial, between nucleoside analogues and interferon plus ribavirin. Our findings mandate the monitoring of lactate, amylase, and body weight in patients coinfecting with HIV and HCV who are receiving antiretroviral and anti-HCV therapy, so as to allow early rec-

TABLE 1. WEIGHT AND BIOCHEMICAL VARIABLES DURING TREATMENT WITH INTERFERON PLUS RIBAVIRIN IN 47 PATIENTS COINFECTED WITH HCV AND HIV AND RECEIVING ANTIRETROVIRAL THERAPY.*

VARIABLE	BASE LINE	3 MONTHS	P VALUE†	6 MONTHS	P VALUE†
Body weight (kg)	70±11	66.3±11	0.01	66.1±11	<0.001
Lactate (mmol/liter)	1.9±0.4	2.2±0.5	0.04	2.25±0.33	0.047
Amylase (U/liter)	78±25	94±35	<0.001	128±187	<0.001
Aspartate aminotransferase (U/liter)	92±59	47±34	<0.001	62±84	<0.001
Alanine aminotransferase (U/liter)	133±83	56±49	<0.001	75±120	<0.001

*Plus-minus values are means ±SD.

†P values are for the comparison with base-line values.

ognition of serious toxic effects. Substantial weight loss should be appreciated as a frequent and characteristic side effect of anti-HCV therapy in patients receiving antiretroviral therapy.

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