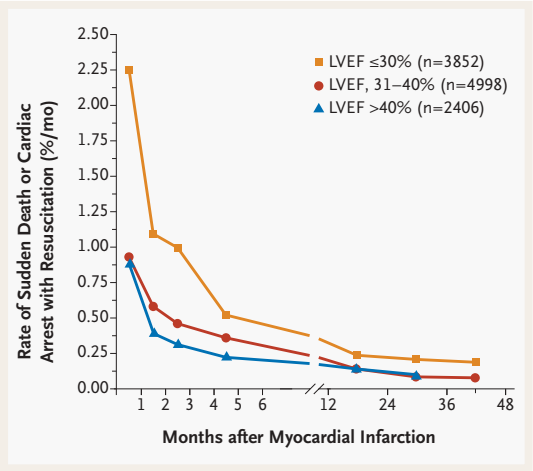
This Week in the Journal

JUNE 23, 2005

ORIGINAL ARTICLE

Timing of Sudden Death after Myocardial Infarction



After myocardial infarction, the risk of sudden death is greatest in the first month and declines thereafter. Patients with an ejection fraction of 30 percent or less are at especially high risk for sudden death, though patients with a higher ejection fraction are still at increased risk. These data will help target preventive strategies to those at highest risk.

SEE P. 2581; EDITORIAL, P. 2638; CME, P. 2662

ORIGINAL ARTICLE

Adjuvant Vinorelbine and Cisplatin for Non–Small-Cell Lung Cancer

In early non–small-cell lung cancer, the standard of care is complete resection followed by observation. This large trial compared observation with adjuvant chemotherapy (vinorelbine plus cisplatin) in early-stage non–small-cell lung cancer and found that survival was improved by the addition of postoperative chemotherapy.

The encouraging results of this trial suggest that adjuvant chemotherapy does have a benefit in patients with early-stage non–small-cell lung cancer who have undergone complete surgical resection of the tumor.

SEE P. 2589; EDITORIAL, P. 2640

ORIGINAL ARTICLE

Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes

This multicenter, phase 2, placebo-controlled trial involved the use of a humanized antibody — ChAglyCD3 — directed against CD3 in the treatment of new-onset type 1 diabetes mellitus. Patients received placebo or ChAglyCD3 for 6 consecutive days and were then followed for 18 months. The insulin dose increased in patients treated with placebo but not in those treated with ChAglyCD3, and residual beta-cell function appeared to be relatively well preserved with ChAglyCD3. This approach may offer a new strategy for the preservation of residual pancreatic function in persons with newly diagnosed type 1 diabetes.

SEE P. 2598; EDITORIAL, P. 2642

ORIGINAL ARTICLE

Peginterferon Alfa-2b and Ribavirin for 12 vs. 24 Weeks in HCV Genotype 2 or 3

Patients with hepatitis C virus (HCV) genotype 2 or 3 were randomly assigned to a standard 24-week course of peginterferon and ribavirin or to therapy of variable duration, in that patients whose condition responded after 4 weeks were treated for 12 weeks rather than 24. The variable-duration strategy was associated with similar response and fewer side effects. This study suggests that a 12-week course of therapy is sufficient for patients with a response after 4 weeks of treatment.

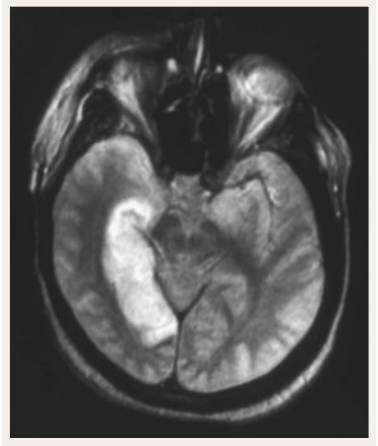
SEE P. 2609; CME, P. 2663

CURRENT CONCEPTS

Vertebrobasilar Disease

About 20 percent of ischemic strokes involve the posterior circulation. The correct diagnosis is often delayed, and workups in patients with symptoms may not always suggest vertebrobasilar disease. This review explains the causes, typical presentations, and characteristic findings of common strokes resulting from disease in the vertebral, basilar, or posterior cerebral arteries. Recommendations are made for treatment with thrombolytic agents and the prophylactic use of antiplatelet agents or anticoagulants.

SEE P. 2618; CME, P. 2661

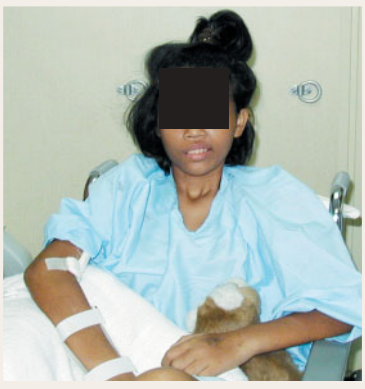


CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

A Girl with Respiratory Distress and Hemiparesis after Surviving a Tsunami

A 17-year-old Indonesian girl was swept up by a tsunami that followed a large earthquake. She aspirated salt water and mud but did not lose consciousness. Two days later, a cough developed; two weeks after the tsunami, she had headache, nausea, and vomiting. One week later, right-sided hemiparesis and aphasia developed, which worsened after several weeks in local hospitals. She was transferred to the U.S. Naval Ship *Mercy* for evaluation and treatment.

SEE P. 2628

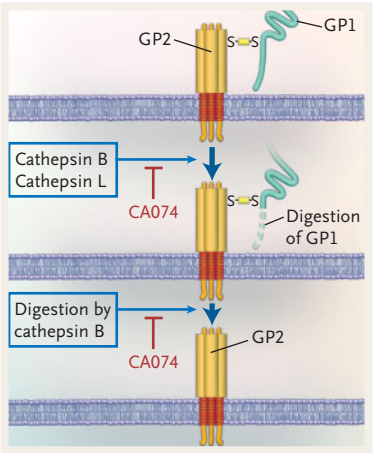


CLINICAL IMPLICATIONS OF BASIC RESEARCH

How Ebola Virus Infects Cells

A recent study provides insight into the way in which Ebola virus enters cells and may therefore suggest a new strategy for therapy.

SEE P. 2645



PERSPECTIVE

Marburg and Ebola — Arming Ourselves against the Deadly Filoviruses

C.J. Peters, M.D.

An interview with Dr. Peters can be heard at www.nejm.org.

As of May 26, 2005, the Angolan Ministry of Health had reported 399 cases of Marburg hemorrhagic fever, 335 of which were fatal. Even as this unprecedented spread of filovirus infection continued, Marburg's sister virus, Ebola, had killed nine people in the Republic of Congo. Although Ebola may now be the better-known sibling, Marburg virus was identified first, in 1967, after an infectious-disease clinician at the university hospital in Marburg, Germany, saw patients with a severe febrile syndrome associated with bleeding from multiple sites on the skin and the mucous membranes and shock. The patients all worked for a pharmaceutical manufacturer, and it later became evident that they had acquired their infection from African green monkeys that were used in the preparation of cell cultures for vaccines. The virus that was isolated in these cases was totally unrelated to any known virus family and turned out to have such a large, bizarre, branching morphology (see diagram) that initially many were even uncertain that it was a virus.

Nine years later, high-fatality outbreaks of unknown origin in Zaire (now known as the Democratic Republic of Congo) and Sudan alarmed the public health community. The viruses that were isolated from the epidemic in Zaire resembled Marburg morphologically and were christened Ebola virus; together with the Marburg virus, they formed the family Filoviridae. In fact, the 1976 outbreaks were caused by two different viruses that were, for unknown reasons, active in separate, remote areas. We now recognize two genera, Marburg virus and Ebola virus, the latter of which has four known species.

These viruses have continued to cause uncommon but alarming epidemics in Africa, which have generally followed a recognizable pattern. One person becomes ill, and the disease begins to percolate through the community at a slow rate. It takes weeks or months to recognize that a filovirus is the cause, because there are no locally available diagnostic tests for these viruses. A clinical diagnosis of dysentery or typhoid commonly results in a delay in efforts to seek the correct diagnosis.

Then, the virus enters the medical care system. The most lethal route of spread is through parenteral infections. Many patients, including those infected with filoviruses, receive injections of various medications at health centers or from pharmacists or healers, and then unsterilized needles and syringes are reused, sometimes to administer medicines drawn from multidose vials. The single-use injection equipment that has been such a boon to the developed world has spelled disaster for the poorest nations. Plastic syringes cannot be heat sterilized and are usually simply rinsed. Needles are usually not sterilized, either. Even when syringes and needles designed for reuse are available, it is common for hospitals to own only a handful of injection sets, which tend to be reused without sterilization simply for logistic reasons. Indeed, it is a poorly kept secret that such reuse is common practice in African countries, where it has been implicated in the spread of hepatitis C and, almost certainly, human immunodeficiency virus (HIV).

Usually, filovirus hemorrhagic fevers predominantly affect adults — especially medical personnel and patients infected in the hospital. Even when an adult patient is cared for at home, children in the household rarely become infected. In the current Angolan epidemic, however, early cases occurred predominantly in children, who were infected in a pediatric ward or clinic through improperly sterilized injection equipment.

Equally important in spreading filoviruses in hospitals is the inadequate use of barriers by nurses.

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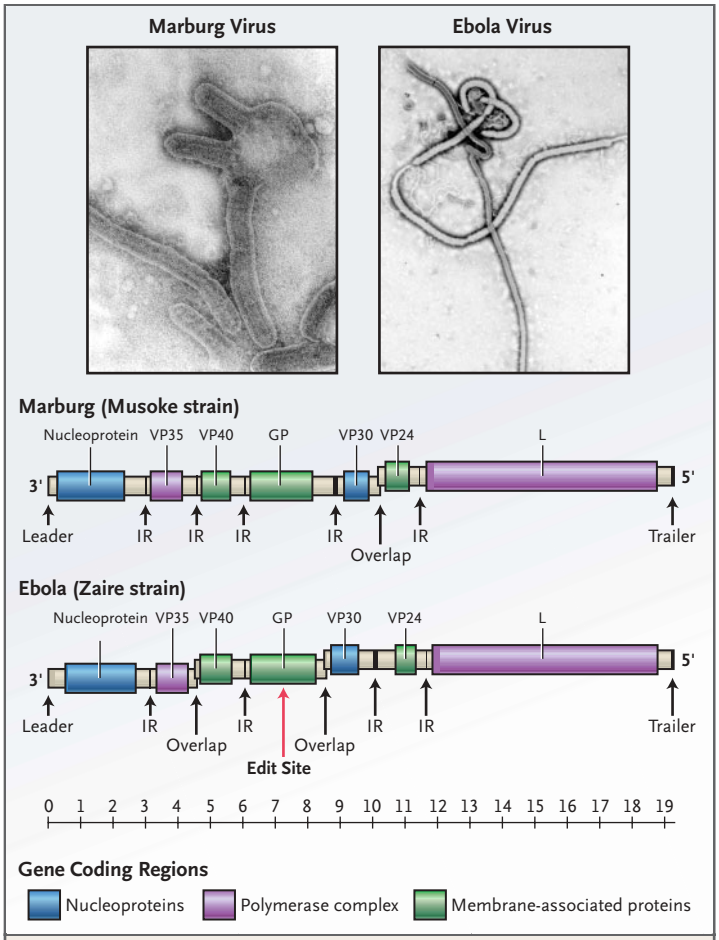

Micrographs courtesy of Frederick A. Murphy, Centers for Disease Control and Prevention.

Electron Micrographs of Marburg and Ebola Viruses and Genomes of the Musoke and Zaire Strains.

IR denotes intergenic region.

Gloves are used only rarely — often not even during surgical procedures — and gowns are not commonly available. Thus, hospital personnel often bear the brunt of these epidemics and participate in the dissemination of disease. In many places, a lack of health care facilities hobbles attempts at control: patients are cared for at home and infect their care providers. In places where appropriate facilities exist, patients with a filovirus disease have little motivation to seek hospitalization, knowing that their neighbors will ostracize their family, that they will probably die in the hospital, and that when they do, they will be whisked away in a body bag — so that their family will be denied the final preparation of the body and the culturally appropriate mourning and burial. And indeed, although hospitalization is important in controlling epidemics, medical institutions have very little to offer individual patients: even supportive care is limited by costs and the fear of infecting staff members.

Most of these epidemics eventually dissipate owing to some combination of the closure of some hospitals because of the attrition of the staff, the institution of good infection-control practices with externally supplied materials in other hospitals, quarantine, and the relatively low transmissibility of filoviruses. Studies have consistently implicated close contact with body fluids or injections as the primary route of interhuman transmission. In addition, extensive viral involvement of the subcutaneous tissues brings the viruses very close to anyone who cares for patients or prepares their bodies for burial. In well-equipped modern hospitals, the incidence of transmission of filoviruses is very low, primarily because unprotected contact with the patients and their blood rarely occurs — thanks in large part to the discipline that has grown up around HIV infection.

We still have no idea how filoviruses are maintained in nature. At first, nonhuman primates were suspected to be the reservoirs, but it is now evident that they, too, are simply targets. They may serve as links to humans, as they did in the original outbreak in Marburg and as they apparently have in the ongoing chain of Ebola virus transmission in the Republic of Congo. To satisfy the increasing appetite for exotic meats, professional hunters now enter forests to kill nonhuman primates and other "bush meat," and others scavenge dead chimpanzees; any of these animals may be infected with a filovirus. Most recent speculation about the source of these viruses has centered around bats — a hypothesis that is supported by a recent Marburg virus epidemic in the Democratic Republic of Congo, in which infection was generally acquired in subterranean gold mines.

Our progress in understanding the filoviruses has been slow because of their rare appearance in nature, the danger they pose to those who study them, and a lack of financial support. Until we began to see them as prime candidates for use in bioterrorism, it was only the occasional epidemic and the remarkable grip of movies and books on the imagination of scientists and the public that motivated research on these viruses. Recently, modern virology and the development of reverse genetic systems have allowed us to understand some of the functions of the different viral proteins (see diagram). The viruses are approximately 80 nm in diameter and 800 to 1100 nm in length, although

they often assume longer and even branching forms. They contain a single negative-sense RNA strand comprising 19 kb. Because they are RNA viruses, they are regarded as having high mutation potential and should be capable of evolving under the appropriate selection pressures.

The high virulence of these viruses seems to be explained in part by the ability of their proteins to defeat the human immune response in several different ways. The most important limb of the innate immune response of the host, which consists of type I interferons, is evaded through the suppression of induction by the VP35 protein and the blocking of interferon action by the VP24 protein. Thus, a crucial host response is not available to resist viral growth, and if interferon is synthesized, it is not able to perform such critical functions as the inhibition of viral growth; the activation of natural killer cells, macrophages, and dendritic cells; and the enhancement of the adaptive immune response. Infected macrophages are induced to secrete cytokines that result in bystander apoptosis of lymphocytes in the tissues that are responsible for the acquired immune response. Circulating infected monocytes express large amounts of tissue factor and initiate disseminated intravascular coagulation, with its attendant tissue damage. Viral infection of endothelial and parenchymal cells of many organs results in further tissue damage, which seems to be mediated directly by the expression of the glycoprotein.

The large amounts of virus and viral antigen in all organs of fatally infected humans and nonhuman primate models of disease suggest that recovery will not readily occur in most cases, even with effective supportive care. In addition, the extreme histologic damage to the immune system and the lack of a detectable humoral immune response in fatal cases suggest that no help from the adaptive immune system is on the way. It has been difficult to detect neutralizing or protective antibodies even in convalescent patients, and if such antibodies as can be detected are administered passively to infected macaques (the best model of human disease), they have generally failed to offer robust protection.

It is likely that any substantial reduction in mortality will require an effective antiviral drug, one of the most important needs in this field. Several prototype vaccines to protect nonhuman primates against Marburg virus infections have shown promise, although numerous attempts to develop vaccines against Ebola virus have failed. Recently, however, two vaccines that solidly protect monkeys have been developed, one involving a vesicular stomatitis virus base and the other using an adenovirus vector. A single injection of the adenovirus construct can protect monkeys, and phase 1 trials of this vaccine have begun. The current filovirus epidemics are in large part a consequence of transmission from the use of unsterilized needles. If such spread were halted, the filoviruses would not present a major problem; and because of hygienic medical practices, they represent little or no natural threat to the developed world. Still, a highly mutable RNA virus that may be transmitted among humans and can be shown in the laboratory to be infectious as an aerosol might conceivably evolve in dangerous directions. We should therefore stop these epidemics promptly whenever they occur and should remain aware that these viruses may someday be harnessed as bioterrorist weapons.

Torcetrapib and Atorvastatin — Should Marketing Drive the Research Agenda?

Jerry Avorn, M.D.

In light of the success of the statin drugs, interest in preventive cardiology has shifted to new frontiers of pharmacologic intervention: defining optimal levels of low-density lipoprotein (LDL) cholesterol, inhibiting cholesterol absorption, addressing the inflammatory component of atherosclerosis, and increasing the levels of protective high-density lipoprotein (HDL) cholesterol. This last approach attracted attention last year when it was reported that a new drug, torcetrapib, could substantially increase levels of HDL cholesterol by inhibiting cholesteryl

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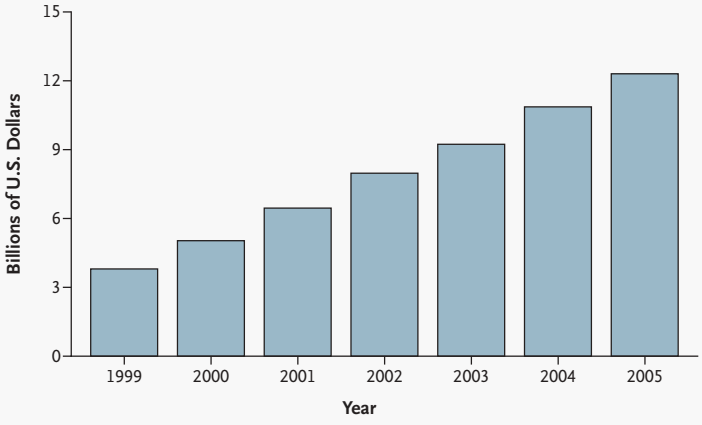
ester transfer protein.[1] The drug was heralded as a novel weapon against heart disease that could be an important clinical tool if its effect on lipids actually reduces the rate of clinical events. Subsequent studies reported in March confirmed the drug's capacity to increase HDL cholesterol markedly.[2] Pfizer, which holds the patent on torcetrapib, is launching several studies to assess the clinical outcomes of treatment with the drug. One study, scheduled to be completed next year, will evaluate the drug's effect on atherosclerotic plaque, as measured by intravascular ultrasonography. In a second trial, investigators will study 13,000 patients over a period of five years to measure rates of myocardial infarction and stroke.

Enthusiasm about this potentially important new therapeutic tool has been tempered by concern about how the company will study and market the drug. Pfizer's trials will study torcetrapib only in combination with the company's widely used atorvastatin (Lipitor), the best-selling drug in the world (see diagram). Sales of Lipitor account for about half of Pfizer's annual profits; the company's patent is due to expire in 2010. Because of this study design, the Food and Drug Administration (FDA) will be presented only with data on the torcetrapib–Lipitor combination as compared with Lipitor alone. If the studies show that the combination is more effective than statin monotherapy, the FDA is likely to approve torcetrapib for use only in a combination product that includes Lipitor — not for separate use or use with another company's statin or with a generic statin — because the only efficacy trial data presented to it will be based on the combination tablet. Such approval would make it impossible for physicians to prescribe the new agent with any other statin — or even with generic atorvastatin when it becomes available in five years.



Total Pfizer Revenues from Lipitor, 1999–2005.
The figure for 2005 is extrapolated from first-quarter revenues. Data are from Pfizer.

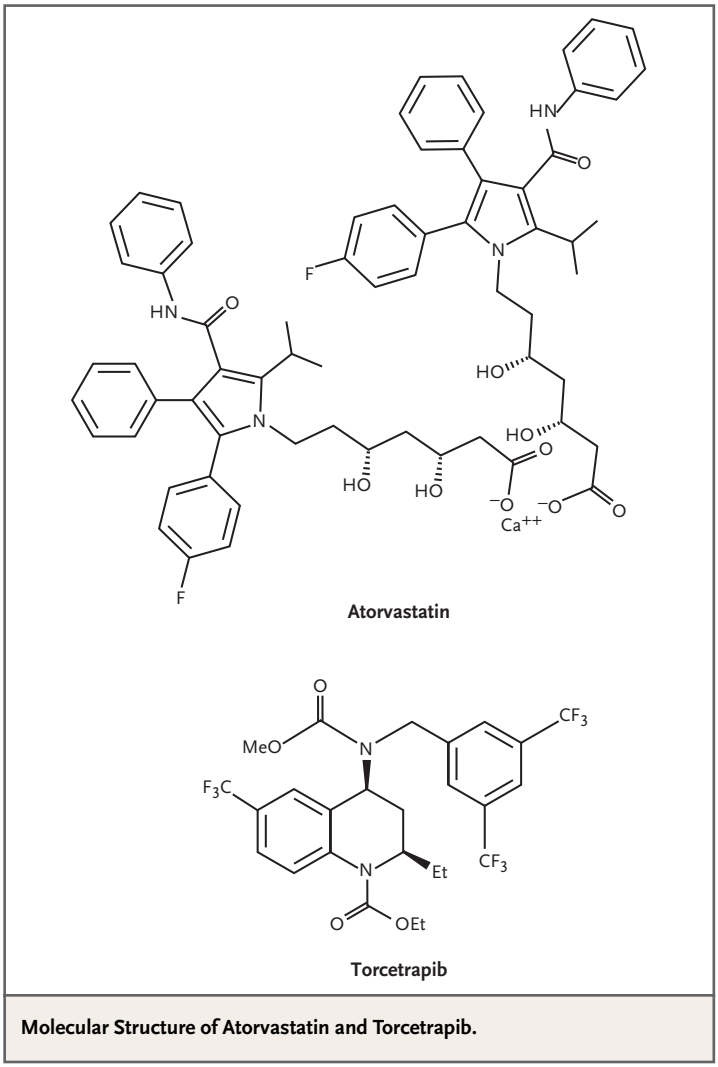
Normally, antitrust laws would prohibit a manufacturer from offering a drug only when "bundled" with another one of its products. It appears that Pfizer will avoid such antitrust prohibitions by having the FDA do its bundling for it. The FDA's acceptance of the proposed trial designs in effect acknowledges that since the new drug is Pfizer's intellectual property, the company's research plans are subject only to its own corporate prerogative. These studies will enroll thousands of patients who are at risk for cardiovascular disease, cost Pfizer millions of dollars, and go on for years. But when they are completed, clinicians, patients, payers, and regulators will still not know how well this important new approach to atherosclerosis performs in combination with any risk-modifying approaches other than Lipitor. Pfizer's position is that it invested in the development of torcetrapib and is paying for its evaluation, so it can study and market the resulting product however it sees fit. As with other costly new drugs, however, research leading to the product's development was also supported by the National Institutes of Health (NIH).[1,3]

High cost will be the most prominent downside of the FDA-sanctioned yoking of the two brand-name drugs. But there will be clinical problems as well: patients who cannot tolerate (or afford) Lipitor will have no way of obtaining torcetrapib for use with another statin that may be better for them. Physicians who want to raise a patient's level of HDL cholesterol — but who do not want to be forced to use Lipitor — will not have access to torcetrapib.

Other research options would have been feasible. Although it makes sense initially to test the additive effects of torcetrapib plus statins over statins alone, a target level of LDL cholesterol could have been set for the trial, with study participants randomly assigned to receive one of several statins — a design that would have produced more generalizable findings. In another scenario, participating clinicians could have reached a target LDL level using the statin of their choice, with patients randomly assigned to receive either torcetrapib or placebo in addition. The FDA often discusses the design of preapproval studies with manufacturers and could have tried to convince Pfizer to implement a study design geared toward better protection of the interests of science,

patients, and even payers. But if such discussions took place, they did not succeed. This may have been the result of the FDA's fear of litigation by the manufacturer, since the owner of a new drug has the legal (although perhaps not the moral) right to conduct its preapproval clinical studies as it sees fit.

The next test for the FDA will come in its response to the results of these trials. What if the combination therapy does reduce the rate of cardiovascular events or atherosclerotic progression better than atorvastatin monotherapy? In principle, the FDA could approve torcetrapib for use in combination with Lipitor, as a single agent for use with other statins, or even alone in uncommon situations. But Pfizer is likely to request approval only for the fixed combination, arguing that this is the sole use of torcetrapib for which adequate trial data are available. The FDA would have to muster uncharacteristic regulatory courage to persuade the company to market the new drug in more than one form; the agency is unlikely to do so and may lack the legal authority. Even if the FDA took such a stand, it could find its options limited by the design of the preapproval research. And in the end, whatever the FDA decided and regardless of the role of public funds in the early development and evaluation of inhibition of cholesteryl ester transfer protein to raise HDL cholesterol, Pfizer, as the owner of the new compound, could still choose to make it available only in combination with Lipitor.



Molecular Structure of Atorvastatin and Torcetrapib.

The torcetrapib controversy brings several longstanding questions about clinical drug research into sharp focus. In the 1990s, as pharmaceutical companies became the most profitable industry group in the nation, their annual research expenditures began to exceed the entire budget of the NIH. Those profits and expenditures did not result in an impressive increase in the rate of discovery of important new drugs by most of the large firms, raising troubling questions about the supposed link between huge cash flows and genuine innovation. Nonetheless, these shifting economic realities helped entrench the dominance of pharmaceutical companies over the research agenda for therapeutics. Growing deficits in the federal budget now place considerable pressure on publicly funded medical research, which will further limit the ability and willingness of the NIH to support applied studies of drug efficacy and safety in the future. Thus, the scientific questions that are asked in both domains will increasingly be defined by the pharmaceutical industry.[4]

The torcetrapib–Lipitor bundling studies illustrate where this trend can lead. The current trial designs may not optimally meet the scientific needs of prescribers, the clinical needs of patients, the economic needs of payers, or the regulatory needs of policymakers. But they superbly meet the business needs of the sponsor — to create new knowledge in a way that will protect the market share of the largest drug company's most important product. A more science-based or patient-centered research design would not have accomplished this goal as well; indeed, any Pfizer official who signed off on such a study might be accused of compromising his or her fiduciary responsibility to the company's shareholders.

This is the predictable consequence of an industry-driven approach to defining the nation's drug-research agenda. But another vision is possi-

ble, and it would reduce rather than increase public expenditures. Well-targeted federally funded medication trials can more than pay for themselves; examples to date include NIH-supported studies of estrogen replacement and of medications for hypertension, which provided important insights into the risks, benefits, and optimal use of these therapies. These needed insights can improve care and save the nation billions in drug expenditures.[5] For instance, if a moderate-size NIH-funded clinical trial of the cardiovascular risks of coxibs had been performed in 2000 and 2001, most of the $2.5 billion per year — about $1 billion annually from public coffers — that was spent on rofecoxib (Vioxx) might have been saved. Other clinical examples abound.

The torcetrapib story suggests that we have become too dependent on manufacturers as the predominant source of our scientific knowledge about the effects of medications. As Medicare prepares for an increasingly unaffordable drug benefit, the best way to contain that public expenditure will be to commit a small fraction of those funds to support such public-interest drug trials, fairly comparing competing therapies (especially costly new ones) with clinically realistic alternatives. With pharmaceutical costs increasing faster than most other health care expenditures, the nation requires studies that will meet the needs of evidence-based prescribing and not just the needs of the pharmaceutical industry. It is not a question of whether we can afford to pay for our own drug trials; it is increasingly evident that we cannot afford not to do so.

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2. Davidson M, McKenney J, Revkin J, Shear C. Efficacy and safety of a novel cholesteryl ester transfer protein inhibitor torcetrapib when administered with and without atorvastatin to subjects with a low level of high-density lipoprotein cholesterol. J Am Coll Cardiol 2005;45:Suppl 1:394A. abstract.
3. Brousseau MF, Diffenderfer MR, Millar JS, et al. Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein A-I metabolism, and fecal sterol excretion. Arterioscler Thromb Vasc Biol 2005;25:1057-64.
4. Avorn J. Powerful medicines: the benefits, risks, and costs of prescription drugs. New York: Alfred A. Knopf, 2004.
5. Fischer MA, Avorn J. Economic implications of evidence-based prescribing for hypertension: can better care cost less? JAMA 2004;291:1850-6.

The Lessons of Vioxx — Drug Safety and Sales

Henry A. Waxman, J.D.

On November 23, 2000, the results of the Vioxx Gastrointestinal Outcomes Research study, known as VIGOR, were published in the *Journal.* This randomized, controlled trial showed that rofecoxib, an inhibitor of cyclooxygenase-2 that had been marketed as Vioxx since May 1999, was associated with fewer gastrointestinal complications than naproxen, a standard nonsteroidal antiinflammatory drug. Unexpectedly, the VIGOR study also showed that the patients who were given rofecoxib had four times as many myocardial infarctions as those who were given naproxen.

This finding of a significant increase in the risk of myocardial infarction was an early signal of a potentially serious safety problem with rofecoxib. Nonetheless, sales remained robust. By the time of rofecoxib's withdrawal from the market in September 2004, after a placebo-controlled study confirmed its cardiovascular risk, more than 100 million prescriptions had been filled in the United States.[1] Tens of millions of these prescriptions were written for persons who had a low or very low risk of gastrointestinal problems.[2]

On May 5, 2005, the Government Reform Committee of the U.S. House of Representatives, on which I serve as the senior Democrat, held a hearing that explored how drugs with serious safety issues, such as rofecoxib, can remain so popular for so long. What we learned illuminated a hidden corner of the health care system: the practices that pharmaceutical manufacturers use to promote their products to physicians.

The pharmaceutical industry spends more than $5.5 billion to promote drugs to doctors each year — more than what all U.S. medical schools spend to educate medical students. Major drug companies employ about 90,000 sales representatives — one for every 4.7 doctors in the United States, according to the American Medical Association.[3] Although substantial marketing expenditures are common

Mr. Waxman is a U.S. Representative from California.

in many industries, the potential effect of drug marketing on health raises special concerns. For years, the industry has justified these expenditures on the grounds that they fund essential education for doctors. According to the Web site of the Pharmaceutical Manufacturers and Research Association, "many physicians learn about new drugs — indeed, about ongoing research in their areas of specialization — largely through information provided by the companies that market new products." But if the primary goal is sales, not education, and the information provided to physicians is slanted or misleading, the health consequences for patients can be serious.

Because of the recent events surrounding rofecoxib, the May 5 hearing of the Government Reform Committee focused on Merck, the manufacturer of Vioxx, which has an excellent reputation within the drug industry and supports many products, such as vaccines, that are medically essential but not very profitable. The company funded VIGOR and appropriately sought to publish its results in a prestigious medical journal. In advance of the committee's hearing, Merck cooperated voluntarily with our request for information, providing more than 20,000 pages of internal company documents. Merck also voluntarily sent a senior executive to testify at the hearing and answer the committee's questions. Yet as we learned, even a company like Merck can direct its sales force to provide clinicians with a distorted picture of the relevant scientific evidence.

On February 7, 2001, the Arthritis Drugs Advisory Committee of the Food and Drug Administration (FDA) met to discuss the VIGOR study. At this meeting, Merck argued that the significant increase in the rate of myocardial infarction (which further analysis had determined to be a fivefold increase) was explained by a protective effect of naproxen, not by any inherent risk posed by its drug. After the FDA's medical reviewer and others expressed concern about this explanation, the advisory committee voted unanimously that physicians should be made aware of VIGOR's cardiovascular results.

The next day, Merck sent a bulletin to its rofecoxib sales force of more than 3000 representatives. The bulletin ordered, "DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS ADVISORY COMMITTEE . . . OR THE RESULTS OF THE . . . VIGOR STUDY." It advised that if a physician inquired about VIGOR, the sales representative should indicate that the study showed a gastrointestinal benefit and then say, "I cannot discuss the study with you."

Merck further instructed its representatives to show those doctors who asked whether rofecoxib caused myocardial infarction a pamphlet called "The Cardiovascular Card." This pamphlet, prepared by Merck's marketing department, indicated that rofecoxib was associated with 1/8 the mortality from cardiovascular causes of that found with other antiinflammatory drugs.

The Cardiovascular Card provided a misleading picture of the evidence on rofecoxib. The card did not include any data from the VIGOR study. Instead, it presented a pooled analysis of preapproval studies, in most of which low doses of rofecoxib were used for a short time. None of these studies were designed to assess cardiovascular safety, and none included adjudication of cardiovascular events. In fact, FDA experts had publicly expressed "serious concerns" to the agency's advisory committee about using the preapproval studies as evidence of the drug's cardiovascular safety.[4]

Persistent physicians who sought additional information about the cardiovascular effects of rofecoxib were directed to send inquiries to the company's headquarters. Merck's response to these physicians highlighted the misleading information from the Cardiovascular Card.

Beyond these specific communications to physicians, our committee also heard evidence of a broad disparity between the evidence-based perspective provided by scientific journals and expert committees, on the one hand, and the sales pitch used by the company's field staff, on the other. Merck instructed its sales representatives, for example, to provide only certain approved study results to doctors. Approved scientific studies were defined as those that provide "solid evidence as to why [doctors] should prescribe Merck products for their appropriate patients." By contrast, those studies that raised safety questions about drugs were considered background studies. Distributing the results of a background study was "a clear violation of Company Policy."

Merck also trained its representatives to identify speakers for educational events who were "opinion leaders" who could provide "favorable" views of the company's products to other doctors. Underlining the promotional nature of these events, Merck instructed its sales representatives to track whether the physicians who attended them subsequently prescribed more Merck drugs.

In addition to providing selective evidence and biased presentations, Merck counseled its representatives to use an array of subliminal selling techniques to affect prescribing — potentially undermining the ability of physicians to choose drugs strictly on the basis of the risks, benefits, and costs for a particular patient. For example, in a training course on selling skills, Merck taught representatives to mimic the words and body language of doctors during sales calls. The curriculum explained that "mirroring is the matching of patterns, verbal and non-verbal, with the intention of helping you enter the customer's world. It is positioning yourself to match the person talking. It subconsciously raises his/her level of trust by building a bridge of similarity."[5]

The committee hearing raised serious questions about the marketing practices used by Merck, but it would be a mistake to restrict the lessons learned to a single company. The testimony we heard indicated that Merck's marketing practices may be less aggressive and more ethical than those of many of its competitors. What is needed is a broad assessment of the ways in which all new drugs are promoted and prescribed in the United States.

As a policymaker, I see a need to enhance the FDA's resources, authority, and oversight of new drugs. The agency does not review all industry promotional material (such as the Cardiovascular Card) quickly; it should have the resources to do so and the authority to require review before dissemination. The FDA should also have more authority to ensure that key information is promptly incorporated into drug labels, and warn doctors about potential safety risks. In the case of a drug such as rofecoxib for which there are serious outstanding concerns about safety, the agency should have the authority to restrict advertising until these concerns have been adequately addressed by further research.

Legislative reform will not be successful, however, without attention to this issue in hospitals and doctors' offices. All the Merck documents discussed above, and many others, are available on our committee's Web site.[5] Practicing physicians, journal editors, and leaders of associations of medical professionals may find these documents useful as they develop new strategies to keep promotional efforts from distorting clinical care.

As we move forward, it is important to recognize that physicians, drug manufacturers, regulators, and policymakers all share the same goal: realizing the vast potential of safe and effective new drugs for improving the health of Americans. We all share responsibility for ensuring that important evidence translates into sound medical practice.

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Tailoring Arthritis Therapy in the Wake of the NSAID Crisis

Nancy J. Olsen, M.D.

In recent months, physicians and patients have been presented with a confusing array of decisions by the Food and Drug Administration (FDA) and the pharmaceutical industry regarding the use of nonsteroidal antiinflammatory drugs (NSAIDs): Merck withdrew its cyclooxygenase-2 (COX-2) inhibitor, rofecoxib, from the market; a closely divided FDA advisory panel recommended continuing the marketing of rofecoxib and other COX-2 inhibitors; and the FDA has requested that Pfizer suspend sales of valdecoxib in the U.S. market, contrary to the recommendation of its advisory committee (although Pfizer is planning discussions with the

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FDA to explore the possibility of resuming these sales). To complicate matters further, new concerns have arisen about the safety of naproxen, an NSAID that is not in the COX-2 class and that has been considered safe enough to be sold over the counter for years. The FDA will now require that black-box warnings about cardiovascular and gastrointestinal risks be included with all these agents.

Although the debate over the safety of these drugs continues, thousands of more circumscribed — and more urgent — debates take place every day in the offices of physicians throughout the country. We are confronted with more questions than we can answer on the basis of the available data, but our patients need advice now, and their concerns cannot be deferred while we wait for the results of more research. Each case must therefore be worked through individually in order to derive the best plan for the particular patient's circumstances. The problem is best framed with a few examples.

One patient in my own rheumatology practice, for example, was a retired professor of medicine who had a complex connective-tissue disorder. Although this disease was kept in relatively good control with low doses of corticosteroids, his joints periodically became inflamed and painful. It didn't happen every day, but it occurred with enough regularity to interfere with his tennis game, his favorite recreational activity. He had found through years of trying various arthritis medications that rofecoxib was the best medication for controlling the problem with his joints. Other conventional and COX-2–selective nonsteroidal drugs simply did not afford him the same degree of relief. Unfortunately, if he took a 25-mg dose of rofecoxib for more than a few days, painful ulcers developed in his mouth. This problem recurred each time he took the drug for several consecutive days, so he was confident that it was drug-related. With some trial and error, he found that one pill taken before he played tennis was sufficient to allow him to get through the day without difficulty and without the side effect of mouth ulceration.

This patient, of course, was better informed than most regarding the potential adverse effects of rofecoxib. But both he and I thought it unlikely that this type of rofecoxib use would have long-term cardiovascular consequences, and his quality of life was improved by the enjoyable physical activity the pain relief permitted him. It is also likely that the rest of his musculoskeletal system benefited substantially from the exercise, so that in his case, the withdrawal of rofecoxib from the market has meant a significant diminution of overall health status.

A second patient whom I have cared for has rheumatoid arthritis that developed two decades ago, before highly active therapeutic agents became available. She has extensive and irreversible joint deformities, has undergone numerous joint operations, and has had recurrent infections. A bleeding ulcer, probably related to long-term use of NSAIDs, resulted in a six-month hospitalization, during which she underwent several surgical procedures and had postoperative wound infections and delayed healing. After being discharged, she strongly desired to return to the naproxen therapy that had worked for her in the past. But the medication that gave this patient the relief from her joint pain could not be prescribed because of the obvious safety risks. She was subsequently given a prescription for a COX-2 inhibitor, which caused no gastrointestinal problems but which she said was never quite as effective as naproxen at alleviating her joint pain.

More recently, I evaluated a woman who had discontinued celecoxib therapy — despite the fact that it had controlled her joint pain — because of the well-publicized questions regarding its safety. Her medical history included recurrent colon polyps, and she had a strong family history of colon cancer. The recent trial of celecoxib suggesting that it increases cardiovascular risk in fact also indicated that it may slow the growth of colon polyps, which would be expected to reduce the patient's risk of colon cancer. I advised her to return to celecoxib, which remains available for prescription use, since its efficacy and safety profile favored its use in a patient such as her.

As these instances demonstrate, there are enough factors to be weighed in the choice of an arthritis medication that the risks and benefits ought to be considered on a case-by-case basis by a physician who knows the patient. Until we have data from large-scale studies, which is unlikely to be soon, it makes sense to weigh the benefit achieved from treatment against the risks of adverse events that are likely to be encountered with traditional NSAIDs (i.e., gastrointestinal side effects) and coxibs (i.e., increased rates of cardiovascular events).

In most cases today, several of these medications are still tried before the most beneficial one is selected. Some patients in my practice claim that rofecoxib was the only drug that worked for their arthritis pain. Although the reasons for such selective re-

sponses remain obscure, it suggests that this drug had some characteristics that distinguished it sufficiently from others in its class that it had unique benefits in some patients. The field of pharmacogenomics is in its infancy, and it will probably be years before we fully understand the biologic basis of these differences. In the meantime, having an array of drugs to choose from, including multiple COX-2–selective agents, would enhance our ability to optimize therapy.

Patients with arthritis and their physicians have covered some of this ground before. A few years ago, questions were raised about the safety of drugs used in the treatment of rheumatoid arthritis, including leflunomide and the tumor necrosis factor inhibitors. Ultimately, these drugs survived those challenges, and they remain mainstays of rheumatoid arthritis therapy. Indeed, it is the availability of these highly active agents that has freed some patients with rheumatoid arthritis from the need for any form of nonsteroidal drugs. We can only hope that still better disease-modifying therapies for conditions such as osteoarthritis are in the offing, so that someday we will be able to offer our patients not just relief from symptoms, but actual remission of disease.

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Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both

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ABSTRACT

BACKGROUND

The risk of sudden death from cardiac causes is increased among survivors of acute myocardial infarction with reduced left ventricular systolic function. We assessed the risk and time course of sudden death in high-risk patients after myocardial infarction.

METHODS

We studied 14,609 patients with left ventricular dysfunction, heart failure, or both after myocardial infarction to assess the incidence and timing of sudden unexpected death or cardiac arrest with resuscitation in relation to the left ventricular ejection fraction.

RESULTS

Of 14,609 patients, 1067 (7 percent) had an event a median of 180 days after myocardial infarction: 903 died suddenly, and 164 were resuscitated after cardiac arrest. The risk was highest in the first 30 days after myocardial infarction — 1.4 percent per month (95 percent confidence interval, 1.2 to 1.6 percent) — and decreased to 0.14 percent per month (95 percent confidence interval, 0.11 to 0.18 percent) after 2 years. Patients with a left ventricular ejection fraction of 30 percent or less were at highest risk in this early period (rate, 2.3 percent per month; 95 percent confidence interval, 1.8 to 2.8 percent). Nineteen percent of all sudden deaths or episodes of cardiac arrest with resuscitation occurred within the first 30 days after myocardial infarction, and 83 percent of all patients who died suddenly did so in the first 30 days after hospital discharge. Each decrease of 5 percentage points in the left ventricular ejection fraction was associated with a 21 percent adjusted increase in the risk of sudden death or cardiac arrest with resuscitation in the first 30 days.

CONCLUSIONS

The risk of sudden death is highest in the first 30 days after myocardial infarction among patients with left ventricular dysfunction, heart failure, or both. Thus, earlier implementation of strategies for preventing sudden death may be warranted in selected patients.

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Sudden death is a catastrophic complication of acute myocardial infarction.[1] Although many patients who die from an acute myocardial infarction do so before reaching the hospital, those admitted remain at substantial risk for ventricular arrhythmias. That risk is greatest in the first few hours, declines rapidly thereafter, and is influenced by the extent of myocardial injury, recurrent ischemia, electrolyte abnormalities, and other factors.[2,3] The success of coronary care units in the 1960s was, in part, related to the early identification and treatment of life-threatening arrhythmias that occurred in the setting of an acute myocardial infarction. Though the risk of sudden death is believed to decrease rapidly after infarction, the extent and time course of this change in risk have not been well studied, especially since the use of coronary reperfusion, beta-blockers, and angiotensin-converting–enzyme inhibitors has become widespread.

Reduced left ventricular function is a major risk factor for death, including sudden death, after myocardial infarction.[4,5] This observation has led to trials of implantable cardioverter–defibrillators (ICDs) in patients with a low left ventricular ejection fraction after infarction.[6] The Multicenter Unsustained Tachycardia Trial (MUSTT) demonstrated the benefit of an ICD in patients with coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and inducible sustained ventricular tachycardia.[7] The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)[8] further showed a benefit of empirical ICD therapy in patients with a left ventricular ejection fraction of 30 percent or less one month or more after myocardial infarction. Although these studies enrolled few patients within six months after they had had a myocardial infarction, the results are reflected in the current American College of Cardiology–American Heart Association guidelines for the management of acute myocardial infarction,[9] which recommend the implantation of an ICD one month or more after myocardial infarction in patients with a left ventricular ejection fraction of 30 percent or less and in those with a left ventricular ejection fraction of 40 percent or less and additional evidence of electrical instability. In contrast, the recently reported Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)[10] did not show that the implantation of an ICD 6 to 40 days after myocardial infarction reduced the risk of death in patients with a left ventricular ejection fraction of 35 percent or less and reduced heart-rate variability. Nevertheless, the risk of sudden death in the early period after myocardial infarction remains high and has not been well studied in the modern era.[11] To better delineate the early and later risk of sudden death after myocardial infarction and the association of these risks with the left ventricular ejection fraction, we studied patients enrolled in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).

METHODS

VALIANT was a randomized, controlled trial of treatment with valsartan, captopril, or both in 14,703 patients with a first or subsequent acute myocardial infarction complicated by heart failure, left ventricular systolic dysfunction, or both.[12] Patients were enrolled between December 1998 and June 2001. All patients had an ejection fraction of no more than 40 percent or clinical or radiologic evidence of heart failure complicating their myocardial infarction. For this analysis, we excluded 94 patients because they had already received an ICD before randomization. All patients gave written informed consent, and the research protocol was approved by the appropriate review boards. The details of the patient population and the protocol, including inclusion and exclusion criteria, have been reported previously.[12]

A central adjudication committee reviewed all deaths and episodes of cardiac arrest with resuscitation in a blinded fashion, using source documentation provided by the site investigators. Deaths were classified as having cardiovascular or noncardiovascular causes, and deaths from cardiovascular causes were further classified as sudden or due to myocardial infarction, heart failure, stroke, or another cardiovascular cause. Sudden death was explicitly defined as death that occurred "suddenly and unexpectedly" in a patient in otherwise stable condition and included witnessed deaths (with or without documentation of arrhythmia) and unwitnessed deaths if the patient had been seen within 24 hours before death but had not had premonitory heart failure, myocardial infarction, or another clear cause of death. Cardiac arrest with resuscitation was defined as cardiac arrest from which a patient regained consciousness and subsequent cognitive function, even briefly.

The median duration of follow-up was 24.7 months. Sudden deaths and episodes of cardiac arrest with resuscitation were combined for this analysis. The left ventricular ejection fraction was determined before randomization (a median of five

days after myocardial infarction) at the clinical site in 11,256 patients: echocardiography was used in 9095, radionuclide ventriculography in 272, and contrast ventriculography in 1889. The analysis of the incidence and timing of sudden death included all patients and was related to the left ventricular ejection fraction in the subgroup of patients for whom information on the ejection fraction was available: 3852 with an ejection fraction of 30 percent or less, 4998 with an ejection fraction of 31 to 40 percent, and 2406 with an ejection fraction of more than 40 percent.

The rates of sudden death were assessed by dividing the events in each period by the number of person-days of exposure and are expressed as the percentage per month. Baseline clinical characteristics were compared with the use of Student's t-test for continuous variables and the chi-square test for categorical variables. The risk of sudden death associated with each decrease of 5 percentage points in the left ventricular ejection fraction was assessed in a Cox proportional-hazards model, with adjustment for all known baseline covariates.

RESULTS

Of 14,609 patients, 1067 (7 percent) had an event: 903 patients died suddenly, and 164 were resuscitated after cardiac arrest. For 643 of the 1067 patients (60 percent), this was the first cardiovascular event after enrollment. Five patients who were resuscitated after cardiac arrest died on the day of resuscitation. The median time to sudden death or cardiac arrest with resuscitation was 180 days after myocardial infarction (interquartile range, 50 to 428). Of the 164 patients who were resuscitated, 108 (66 percent) were alive at six months and 93 (57 percent) were alive at the end of the trial. As compared with surviving patients without events, patients who died suddenly or had cardiac arrest with resuscitation were significantly older; had higher baseline systolic and diastolic blood pressures, baseline heart rate, and Killip class; had a lower left ventricular ejection fraction; were more likely to have a history of diabetes or hypertension; and were less likely to have been treated with reperfusion therapy, amiodarone, or beta-blockers (Table 1). The differences between patients who died suddenly or were resuscitated after cardiac arrest and those who died of other causes were much less clinically apparent.

During the first 30 days after myocardial infarction, 126 patients died suddenly and 72 patients were resuscitated after cardiac arrest (representing 19 percent of all patients with such events during the trial), for an event rate of 1.4 percent per month (95 percent confidence interval, 1.2 to 1.6 percent). Eighty-three percent of sudden-death events from which the patients were not resuscitated occurred after hospital discharge. Of the patients who were resuscitated during the first 30 days after myocardial infarction, 74 percent were alive at 1 year. Event rates and the cumulative incidence of events during various periods in the study are shown in Table 2. The rate of sudden death or cardiac arrest with resuscitation decreased precipitously during the first year, declining to 0.14 percent per month (95 percent confidence interval, 0.11 to 0.18 percent) after year 2.

Figure 1 shows the Kaplan–Meier estimates of the rate of sudden death or cardiac arrest with resuscitation according to the left ventricular ejection fraction in patients in whom the ejection fraction was measured. The increased early incidence of these events was most apparent among patients with an ejection fraction of 30 percent or less: the incidence rate during the first 30 days was 2.3 percent per month (95 percent confidence interval, 1.8 to 2.8 percent) (Fig. 1 and 2). Of the 156 sudden deaths or episodes of cardiac arrest with resuscitation that occurred during the first 30 days, 85 occurred among the 3852 patients with an ejection fraction of 30 percent or less (54 percent; 1 percent of all patients with a known left ventricular ejection fraction). Of the 3852 patients with an ejection fraction of 30 percent or less, 399 (10 percent) died suddenly or had cardiac arrest with resuscitation during the trial, as compared with 295 of the 4998 patients with an ejection fraction of 31 to 40 percent (6 percent) and 119 of the 2406 patients with an ejection fraction of more than 40 percent (5 percent). Among the patients with a known left ventricular ejection fraction, 49 percent of all sudden deaths or cardiac arrests with resuscitation occurred in patients with an ejection fraction of 30 percent or less, and this proportion remained relatively constant throughout follow-up.

Among the 399 patients with an ejection fraction of 30 percent or less who died suddenly or had cardiac arrest with resuscitation, 85 (21 percent) did so during the first 30 days after myocardial infarction, as compared with 50 of 295 such patients with an ejection fraction of 31 to 40 percent (17 percent) and 21 of 119 such patients with an ejection fraction of more than 40 percent (18 percent). Nevertheless, even among patients with an ejection frac-

Table 1. Baseline Characteristics of the Patients, According to the Outcome.*

Characteristic	Sudden Death or Cardiac Arrest with Resuscitation (N=1067)	Death from Cause Other Than Sudden Death (N=1905)	P Value	Survival Free of Sudden Death or Cardiac Arrest with Resuscitation (N=11,637)	P Value†
Age (yr)	67.8±11.2	71.4±10.3	<0.001	63.5±11.7	<0.001
Male sex (%)	67	61	0.002	70	0.04
Blood pressure (mm Hg)					
Systolic	125.1±18.2	123.5±17.5	0.02	122.3±17.0	<0.001
Diastolic	73.3±12.0	71.9±11.9	0.002	72.3±11.1	0.008
Heart rate (beats/min)	78.1±13.6	78.9±13.7	0.10	75.6±12.5	<0.001
Body-mass index	27.7±5.7	27.1±5.0	0.007	28.0±5.3	0.04
Killip class (%)			0.13		<0.001
I	19	17		30	
II	46	47		49	
III	26	26		15	
IV	9	10		5	
Clinical or radiologic evidence of CHF at entry (%)	83	85	0.10	75	<0.001
Prior myocardial infarction (%)	45	41	0.08	24	<0.001
History of hypertension (%)	64	64	0.96	53	<0.001
History of diabetes (%)	31	32	0.42	21	<0.001
Beta-blocker (%)	61	57	0.07	73	<0.001
Amiodarone (%)	20	19	0.73	8	<0.001
Primary PCI (%)	8	8	0.34	17	<0.001
Thrombolytic therapy (%)	24	25	0.32	38	<0.001
Primary PCI or thrombolytic therapy (%)	30	32	0.25	49	<0.001
LVEF	0.32±0.10	0.33±0.10	0.06	0.36±0.10	<0.001

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Percentages may not sum to 100 because of rounding. CHF denotes congestive heart failure, PCI percutaneous coronary intervention, and LVEF left ventricular ejection fraction.
† P values are for the comparison with sudden death or cardiac arrest with resuscitation.

tion of more than 40 percent, the rate of sudden death or cardiac arrest with resuscitation was more than six times as high in the first month as after one year. Although the incidence of sudden death or cardiac arrest with resuscitation declined markedly over time in all groups, the relative risk of these events remained two to three times as high as among patients with a left ventricular ejection fraction of 30 percent or less as among patients with an ejection fraction of more than 40 percent, although overall, the absolute rate after two years was substantially lower than during the early period. When the left ventricular ejection fraction was considered as a continuous variable, each decrease of 5 percentage points in the ejection fraction was associated with a 21 percent increase in the risk of sudden death or cardiac arrest with resuscitation during the first 30 days after myocardial infarction (hazard ratio, 1.21; 95 percent confidence interval, 1.10 to 1.30), after adjustment for all known baseline covariates.

DISCUSSION

The results of our analysis confirm that patients with left ventricular dysfunction, heart failure, or both after myocardial infarction are at high risk for sudden death or cardiac arrest with resuscitation. The absolute risk is greatest in the early period after myocardial infarction and among patients with the lowest ejection fraction and declines significantly over time, reaching a steady state at approximately

Table 2. Event Rate and Cumulative Incidence of Events during Follow-up.*

Time after Myocardial Infarction	No. at Risk at Beginning of Interval	No. Who Died of Any Cause during Interval	Sudden Death or Cardiac Arrest with Resuscitation		
			No. of Patients	Event Rate	Cumulative Incidence
				%/mo (95% CI)	%
0–30 Days	14,609	589	198	1.4 (1.2–1.6)	1.4
>1–6 Mo	13,997	767	340	0.50 (0.45–0.55)	2.5
>6–12 Mo	13,157	509	211	0.27 (0.23–0.31)	1.6
>1–2 Yr	12,622	754	240	0.18 (0.16–0.20)	2.1
>2–3 Yr	7,926	244	75	0.14 (0.11–0.18)	1.7

* CI denotes confidence interval.

one year. The risk was increased despite the fact that all patients, according to the study design, were receiving inhibitors of the renin–angiotensin system and the majority were receiving beta-blockers and aspirin.

Several measures may identify patients at highest risk for sudden death in the first year after myocardial infarction.[3,13,14] These are an assessment of the frequency or severity of arrhythmia, including the incidence of premature ventricular contractions, nonsustained ventricular tachycardia, dispersion of the QT interval, and late potentials on signal-averaged electrocardiograms; measures of autonomic function; and the results of invasive electrophysiological testing.[15-17] The left ventricular ejection fraction, an independent risk factor for sudden death, is currently the most widely used and robust clinical determinant of risk after infarction and has become the basis for determining a patient's eligibility for ICD therapy.[9] However, it is poor at distinguishing between patients who will die from arrhythmia and those who will die of other cardiovascular causes.[18] In VALIANT, patients who died suddenly were similar to those who died of other causes. Other causes of death included pump failure, recurrent myocardial infarction, procedure-related causes, other cardiac causes, and noncardiac causes, which were relatively rare in this population. Baseline characteristics that were associated with an increased risk of death from other causes were also associated with an increased risk of sudden death. Our inability to distinguish patients who died suddenly from those who died of other causes may reflect our lack of more sophisticated measures of the risk of arrhythmia in this study.

The other key determinant of the risk of sudden death is the time after myocardial infarction. The absolute risk of sudden death is highest in the first year after myocardial infarction. Our data suggest that this risk is greatest within the first week after myocardial infarction and falls rapidly within the first month. The increased early rate of sudden death was highest among patients with the lowest left ventricular ejection fraction, but the high incidence was not restricted to patients with the lowest left ventricular ejection fraction. Indeed, the incidence of sudden death in the group with the highest ejection fraction was greater in the first 30 days than was the incidence of sudden death in the group with the lowest ejection fraction after 90 days. Moreover, patients who died suddenly or had cardiac arrest with resuscitation were in clinically stable con-

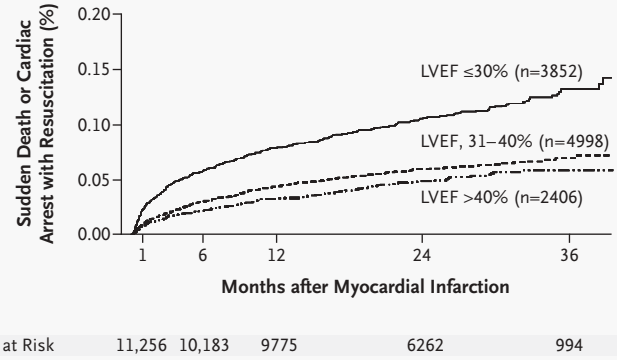

Figure 1. Kaplan–Meier Estimates of the Rates of Sudden Death or Cardiac Arrest with Resuscitation, According to the Left Ventricular Ejection Fraction (LVEF).

The analysis was restricted to patients for whom data on LVEF were available.

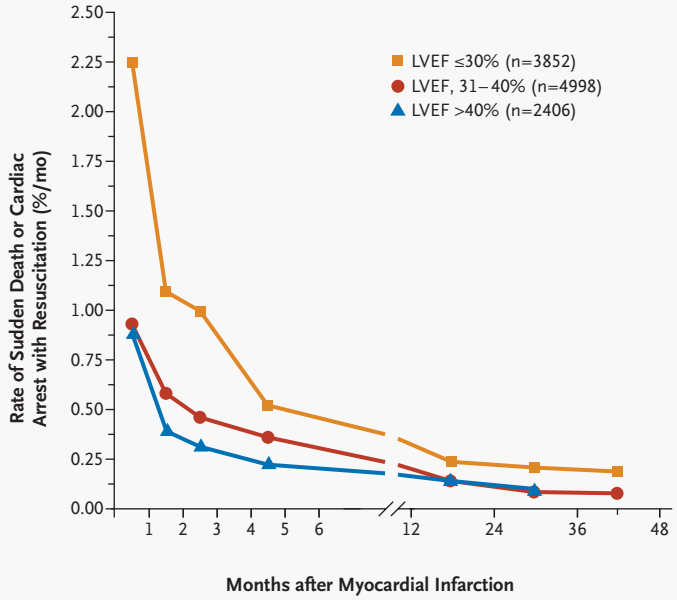

Figure 2. Rate of Sudden Death or Cardiac Arrest with Resuscitation over the Course of the Trial in the Three Categories of Left Ventricular Ejection Fraction (LVEF).

The analysis was restricted to patients for whom data on LVEF were available. The average rate (percentage per month) is shown at the midpoint of each period.

dition and many had recently been discharged from the hospital. Thus, to prevent sudden death after infarction, the ideal strategy must also take into account patients with a better-preserved left ventricular ejection fraction (more than 40 percent).

The discriminatory effect of the left ventricular ejection fraction appears to be greatest in the first six months after myocardial infarction. Among patients who survived beyond one year, the annualized rate of sudden death was still highest in the group with the lowest left ventricular ejection fraction but was fairly similar among the three ejection-fraction groups, although the relative risk remained higher in the groups with a lower ejection fraction. This observation, however, should be tempered by the fact that patients who survive are already at lower risk. Also, ventricular function was measured relatively early after infarction, and in some patients, substantial recovery of ventricular function may have occurred with a concomitant decrease in the risk of sudden death. An additional decline in the left ventricular ejection fraction may occur over time, and the risk of sudden death at a particular time after myocardial infarction is more likely to be related to the ejection fraction at that time than to the ejection fraction in the periinfarction period.

Although our findings suggest that a strategy of treating a greater proportion of patients early and focusing on those with a low left ventricular ejection fraction later might be the most efficient approach to minimizing the risk of sudden death after myocardial infarction, the recently reported DINAMIT showed no benefit of implanting an ICD 6 to 40 days after myocardial infarction in patients with an ejection fraction of 35 percent or less and evidence of reduced heart-rate variability.[10] Indeed, in that trial, a decrease in the rate of death from arrhythmia was offset by an increase in the rate of death from other causes.[19] The DINAMIT findings thus did not provide support for the use of early ICD therapy in a high-risk population after myocardial infarction and underscore the fact that patients at increased risk for sudden death from arrhythmia are also at increased risk for death from other causes.

Although it is difficult to reconcile the absence of a benefit in DINAMIT with the substantially increased risk of sudden death we observed in the early post-infarction period, there were a number of important differences between the two studies. Although DINAMIT enrolled patients with a lower overall left ventricular ejection fraction than did VALIANT, the average time to enrollment was 18 days after myocardial infarction — 13 days later than the average enrollment date in VALIANT — and thus, DINAMIT may have selected for patients already at lower risk for sudden death. Moreover, at 7.2 percent per year, the overall mortality rate was lower in DINAMIT than in VALIANT. Although the rate of death from arrhythmia in the DINAMIT control group was similar to the rate of sudden death in VALIANT (3.5 percent and 3.7 percent per year, respectively), the true rate of death from arrhythmia in our study may have been much higher, since only unexpected deaths were categorized as sudden, thereby excluding patients with fatal arrhythmia in the setting of myocardial infarction or pump failure. Alternatively, DINAMIT, with only 120 deaths, may have been statistically underpowered to demonstrate a clinically important difference between groups, an interpretation that would suggest the need for additional studies of ways to prevent sudden death from arrhythmia in the early period after infarction.

It remains unclear whether therapies targeted at a high-risk population soon after infarction would reduce the risk of sudden unexpected death, but

our data provide a rationale for considering early-intervention strategies, including short-term therapies, in selected patients at risk. This is supported by the fact that the majority of our patients (74 percent) who were resuscitated during the first 30 days were alive at 1 year. In addition, although our data suggest that the overall risk of sudden death or cardiac arrest with resuscitation increases with a decreasing left ventricular ejection fraction, even in patients with an ejection fraction of more than 40 percent, the risk of sudden death or cardiac arrest with resuscitation was six times as high in the first 30 days as at 1 year, suggesting a potential role for early short-term intervention, even in lower-risk patients. For example, if all sudden deaths could be prevented, a strategy of treating everyone for 30 days and only those with a left ventricular ejection fraction of 30 percent or less beyond 30 days in the VALIANT study would potentially have prevented or postponed 507 deaths, as compared with 317 deaths with the use of the currently recommended strategy of treating only those with an ejection fraction of 30 percent or less beyond 30 days. This approach may not be practical on the basis of current ICD technology, but such an approach might be practical and cost-effective in the future, although it must be noted that current Medicare regulations do not allow for payment for ICD therapy before 40 days after myocardial infarction.[6]

A number of limitations of this analysis should be noted. First, the left ventricular ejection fraction was measured locally, not centrally, although local estimation of the ejection fraction is used to make clinical decisions. Second, some patients identified as having died suddenly may have died from causes such as aortic dissection, pulmonary embolism, stroke, and especially, reinfarction; in the case of reinfarction, sudden death may still be due to arrhythmia.[20] Also, since our definition of sudden death specified prior stability, we may have excluded many deaths from arrhythmia that occurred in the setting of myocardial infarction or heart failure. Finally, although our data may help guide interventional strategies that reduce risk, we did not assess the efficacy of such strategies.

In summary, we demonstrated that the risk of sudden death is highest soon after myocardial infarction — particularly during the first 30 days. This risk is greatest among patients with the lowest left ventricular ejection fraction (30 percent or less), but even patients with a high ejection fraction (more than 40 percent) are at substantially increased risk in the early post-infarction period, as compared with the subsequent risk, and the discriminatory effect of the left ventricular ejection fraction declines over time. Although it is not known whether early ICD therapy would reduce these risks, taken in the context of recent data demonstrating the benefits of ICD therapy in high-risk patients,[21] our data suggest the need to consider implementing strategies to prevent sudden death in selected patients before the time recommended by current guidelines.

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CORRECTION

Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both

Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both . On page 2581, lines 9 and 10 in the Results section of the Abstract should have stated that ``83 percent of all patients who died suddenly in the first 30 days did so after hospital discharge,'' rather than ``83 percent of all patients who died suddenly did so in the first 30 days after hospital discharge,'' as printed. We regret the error.

ORIGINAL ARTICLE

Vinorelbine plus Cisplatin vs. Observation in Resected Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

We undertook to determine whether adjuvant vinorelbine plus cisplatin prolongs overall survival among patients with completely resected early-stage non–small-cell lung cancer.

METHODS

We randomly assigned patients with completely resected stage IB or stage II non–small-cell lung cancer to vinorelbine plus cisplatin or to observation. The primary end point was overall survival; principal secondary end points were recurrence-free survival and the toxicity and safety of the regimen.

RESULTS

A total of 482 patients underwent randomization to vinorelbine plus cisplatin (242 patients) or observation (240); 45 percent of the patients had pathological stage IB disease and 55 percent had stage II, and all had an Eastern Cooperative Oncology Group performance status score of 0 or 1. In both groups, the median age was 61 years, 65 percent were men, and 53 percent had adenocarcinomas. Chemotherapy caused neutropenia in 88 percent of patients (including grade 3 febrile neutropenia in 7 percent) and death from toxic effects in two patients (0.8 percent). Nonhematologic toxic effects of chemotherapy were fatigue (81 percent of patients), nausea (80 percent), anorexia (55 percent), vomiting (48 percent), neuropathy (48 percent), and constipation (47 percent), but severe (grade 3 or greater) toxic effects were uncommon (<10 percent). Overall survival was significantly prolonged in the chemotherapy group as compared with the observation group (94 vs. 73 months; hazard ratio for death, 0.69; P=0.04), as was relapse-free survival (not reached vs. 46.7 months; hazard ratio for recurrence, 0.60; P<0.001). Five-year survival rates were 69 percent and 54 percent, respectively (P=0.03).

CONCLUSIONS

Adjuvant vinorelbine plus cisplatin has an acceptable level of toxicity and prolongs disease-free and overall survival among patients with completely resected early-stage non–small-cell lung cancer.

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LUNG CANCER IS THE LEADING CAUSE OF death from cancer in North America.[1] For early-stage non–small-cell lung cancer, surgical resection is the treatment of choice, yet five-year survival ranges from only 30 percent to 60 percent.[2] Recurrences leading to death occur mainly in extrathoracic sites after complete resection. Therefore, there is a need for effective systemic therapy to reduce the risk of recurrence and improve survival.[2,3]

A British Medical Research Council meta-analysis of cisplatin-based chemotherapy after surgery for stage I through stage III non–small-cell lung cancer showed a 13 percent reduction in the risk of death and an absolute improvement in survival of 5 percent at five years, but when compared with observation alone after surgery, the difference was statistically insignificant ($P=0.08$).[4] More recently, a large international trial of adjuvant chemotherapy that used cisplatin plus either a vinca alkaloid or etoposide (International Adjuvant Lung Cancer Trial [IALT]) reported similar results, with a 4.1 percent improvement in five-year survival (hazard ratio, 0.86; $P<0.03$).[5] With such small gains in survival, neither physicians nor their patients have been convinced that the toxicity of adjuvant chemotherapy is justified in the treatment of non–small-cell lung cancer. Thus, observation alone has been the standard of care after resection of early-stage non–small-cell lung cancer.

Newer chemotherapeutic agents (vinorelbine, gemcitabine, taxanes, and camptothecins), when coupled with a platinum derivative, have significantly increased response and overall survival rates as compared with previous regimens in advanced non–small-cell lung cancer.[6,7] Trials confirming the superior efficacy of vinorelbine in combination with platinum as compared with previous combinations were published in the early 1990s.[6,7] Simultaneously, serotonin-receptor antagonists were shown to be effective in reducing the severity of cisplatin-induced emesis.[8] Thus, an outpatient regimen of vinorelbine plus cisplatin as adjuvant chemotherapy, administered with antiemetics and supportive care, was considered an excellent choice and led to the initiation of the National Cancer Institute of Canada Clinical Trials Group JBR.10 trial in patients with completely resected stage IB or stage II non–small-cell lung cancer.

METHODS

STUDY DESIGN

This study was a North American intergroup, phase 3, randomized trial of adjuvant vinorelbine plus cisplatin after resection of stage IB or stage II non–small-cell lung cancer. It was begun in April 1994 in Canada. The American cooperative groups (Cancer and Leukemia Group B [CALGB], Southwest Oncology Group [SWOG], and Eastern Cooperative Oncology Group [ECOG]) joined in 1998. Within six weeks after surgery, eligible patients were randomly assigned in a 1:1 ratio[9] to adjuvant vinorelbine plus cisplatin or observation. Patients were stratified according to nodal status (N0 vs. N1) and the presence or absence of a *ras* mutation. The primary end point was overall survival. Secondary end points included recurrence-free survival and the safety, toxicity, and quality of life associated with this regimen.

The protocol was approved by the institutional review boards at all the institutions, and all patients provided written informed consent. Funding was provided by the National Cancer Institute of Canada, the National Cancer Institute of the United States, and GlaxoSmithKline. Data were collected, managed, and analyzed by the National Cancer Institute of Canada Clinical Trials Group. GlaxoSmithKline had no part in writing the manuscript but did review an early draft, with no right to change the text or its conclusions. There was no contractual obligation with GlaxoSmithKline with respect to the decision to submit the manuscript for publication, and the company had no influence on the content or preparation of this article. Dr. Winton, the study chair, vouches for the accuracy and completeness of the data.

ELIGIBILITY CRITERIA

Patients 18 years of age or older with completely resected T2N0, T1N1, or T2N1 non–small-cell lung cancer with acceptable baseline characteristics and an ECOG performance status of 0 or 1 were eligible. All patients had a preoperative computed tomographic scan, and intraoperative mediastinal lymph-node resection or biopsy of nodes that were 1.5 cm or larger was mandatory. Patients with incomplete preoperative or intraoperative staging, incomplete resection, wedge or segmental resec-

tion, involvement of tracheobronchial angle nodes (station 10) or more central mediastinal nodes, mixed histologic features, a T3 tumor, or diffuse lobar or multifocal bronchioalveolar carcinoma and patients who had had breast cancer, renal-cell carcinoma, melanoma, or other cancers treated within the previous five years were ineligible. Patients with clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders were also ineligible.

RANDOMIZATION AND TREATMENT REGIMEN

Treatment started within two days after randomization. A regimen of 50 mg of cisplatin per square meter of body-surface area on days 1 and 8 every 4 weeks for four cycles and 25 mg of vinorelbine per square meter weekly for 16 weeks was prescribed. The protocol originally called for 30 mg of vinorelbine per square meter, but the dose was amended in August 1995 because of hematologic toxicity (only 18 patients received 30 mg of vinorelbine per square meter). All patients received ondansetron, commonly with a corticosteroid, and chemotherapy was adjusted for toxicity according to protocol guidelines.

FOLLOW-UP

Follow-up clinical examinations and chest radiography were performed every three months for three years and every six months thereafter. Data assessing quality of life were collected prospectively in both groups, but the details of the findings and data analysis are beyond the scope of this article.

ras EVALUATION

Participating centers submitted fresh-frozen primary tumor or paraffin-embedded blocks of tissue specimens to a central laboratory for *ras* mutation analysis of codons 12, 13, and 61 of the *H-ras*, *K-ras*, and *N-ras* genes by allele-specific oligonucleotide hybridization. The results were confirmed by sequencing.[10]

STATISTICAL ANALYSIS

A sample size of 450 patients recruited over a period of 6.75 years, with less than 1 year of follow-up, and 198 events (deaths) were required to provide the study with 80 percent power to detect a 10 percent improvement in survival (from an estimated 3-year survival rate of 60 percent) with a one-sided 5 percent significance level. Two planned interim analyses were conducted in March 2000 and March 2002, after 64 and 122 deaths, respectively. The database was locked in April 2004, and all randomized patients were included in the final analysis, which was based on the intention-to-treat method. Patients who received any protocol treatment were included in toxicity analyses.

Median survival, 95 percent confidence intervals, and Kaplan–Meier estimates of recurrence-free survival and overall survival were calculated according to standard methods.[11-13] The Cox regression model, stratified according to nodal status — including the status of *ras* mutations (unknown vs. mutation vs. wild type) as a covariate — was used to test the difference in overall and recurrence-free survival between the study groups.[13] For the primary analysis of overall survival, the stagewise ordering method was used to obtain the P value adjusted for the two planned interim analyses.[14] An unadjusted log-rank test and an exploratory, stratified Cox regression model analysis, adjusted for *ras* status, age, sex, performance status (ECOG 0 or 1), extent of resection, and histologic features, were performed. To test whether treatment effects were homogeneous across the stratification factors, subgroup analyses of overall and recurrence-free survival with the use of proportional-hazards models with interaction terms were included.[13] All P values reported are the result of two-sided tests.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between July 1994 and April 2001, 532 patients were registered, and 482 were randomly assigned to observation (240 patients) or chemotherapy (242). Fifty registered patients (9.4 percent) never underwent randomization, owing to patient refusal (36 patients), postoperative death (2), intercurrent illness (4), decreased performance status (2), metastases (2), and ineligibility (4). Forty-one patients (8.5 percent) — 22 in the observation group and 19 in the chemotherapy group — who underwent randomization did not fully meet eligibility criteria: 7 had incomplete staging or screening data, 15 had tumors that were more advanced than stage II, 18 had abnormal laboratory results, and 1 had incomplete resection.

Follow-up ranged from 1.5 to 9.3 years (median,

5.1 years) in the chemotherapy group and 0.4 to 9.0 years (median, 5.3 years) in the observation group. Three patients (0.6 percent) were lost to follow-up, two in the treatment group at 6.3 and 7.0 years after randomization and one in the observation group at 4.1 years after randomization.

The baseline characteristics of the patients are shown in Table 1. The two groups were evenly distributed with respect to important prognostic variables, including age, sex, ECOG performance status, and histologic features.

Table 1. Baseline Characteristics of the Randomized Patients.

Characteristic	Observation (N=240)	Chemotherapy (N=242)
Age (yr)		
Median	61	61
Range	34–78	35–82
Male sex (%)	64	66
ECOG performance status (%)*		
0	49	50
1	51	50
Histologic features (%)		
Adenocarcinoma	53	53
Squamous	38	37
Undifferentiated	7	8
Mixed	2	2
ras status (%)		
Mutation present	24	24
Wild type	70	68
Unknown	6	8
Pathological tumor stage (%)		
1	13	16
2	87	84
Nodal status (%)		
0	45	46
1	55	54
Stage (%)		
IB	45	46
IIA	13	16
IIB	42	38
Extent of resection (%)		
Lobectomy	71	66
Bilobectomy	7	9
Pneumonectomy	22	25

* ECOG denotes Eastern Cooperative Oncology Group.

DELIVERY AND TOXICITY OF CHEMOTHERAPY

Data concerning drug delivery, treatment compliance, and quality of life were reported previously.[15,16] At least one dose of medication was received by 231 patients (95.5 percent); 11 of the patients randomly assigned to vinorelbine plus cisplatin (4.5 percent) did not receive chemotherapy (9 patients refused treatment, 1 was ineligible, and 1 was randomly assigned to observation erroneously) (Table 2). The median number of cycles delivered was three. Fifty-eight percent of the patients received three or more cycles of cisplatin, 77 percent had at least one dose reduction or omission, and 55 percent required one dose delay or more, most related to neutropenia at the expected time of vinorelbine administration on day 15 (cycle week 3). Seventy-three of the patients who received at least one dose (32 percent) required hospitalization — 16 (7 percent) for administration of chemotherapy, 14 (6 percent) for reasons unrelated to treatment (with death in 1 patient), and 43 (19 percent) for medical problems related to toxicity (with death in 1 patient).

Neutropenia was the most common severe toxic effect of chemotherapy; 73 percent of patients had grade 3 or 4 neutropenia, 7 percent had grade 3 or 4 anemia, and 1 percent had grade 3 thrombocytopenia (Table 3). Colony-stimulating factors were administered to 15 percent of the patients and febrile neutropenia occurred in 7 percent. Severe nonhematologic toxic effects from chemotherapy were uncommon. Grade 3 or 4 anorexia, nausea, or vomiting was reported by 10 percent, 10 percent, and 7 percent of the patients, respectively. Grade 3 or 4 sensory neurotoxicity, motor neurotoxicity, or hearing loss was observed in 2 percent, 3 percent, and 2 percent, respectively.

Two patients (0.8 percent) died because of treatment-related toxicity — one during chemotherapy from sepsis secondary to febrile neutropenia, and one six months after chemotherapy from interstitial lung disease, first documented during treatment.

RELAPSE-FREE AND OVERALL SURVIVAL

Recurrence was documented in 206 patients (42.7 percent) — 87 in the group assigned to vinorelbine and cisplatin (36.0 percent) and 119 in the observation group (49.6 percent) (P=0.003). The Kaplan–Meier estimates of recurrence-free survival are shown in Figure 1A. Chemotherapy significantly prolonged recurrence-free survival as compared with observation (hazard ratio for recurrence, 0.60; 95 percent confidence interval, 0.45 to 0.79;

Table 2. Delivery of Chemotherapy for Patients Randomly Assigned to Vinorelbine plus Cisplatin.

Delivery Status*	Total No. of Patients	Percent Randomized (N=242)	Percent Treated (N=231)
Randomized	242	100	96
Never treated	11	4	
Day 1 of cycle 1 only	27	11	12
Completed at least cycle 1	204	84	88
Completed cycle 2	156	64	68
Completed cycle 3	133	55	58
Completed cycle 4	110	45	48

* A completed cycle indicates that the patient received both planned doses of cisplatin for that cycle.

Table 3. Drug-Related Adverse Events among Patients Who Received at Least One Dose of Vinorelbine plus Cisplatin.

Adverse Event	Vinorelbine plus Cisplatin*	
	Any Grade	Grade 3 or 4
	percent	
General		
Fatigue	81	15
Anorexia	55	10
Alopecia	32	0
Local toxicity	35	3
Gastrointestinal		
Diarrhea	23	<1
Nausea	80	10
Vomiting	48	7
Constipation	47	3
Infectious		
Infection	22	1
Febrile neutropenia	7	7†
Neurotoxic		
Hearing loss	21	2
Sensory neuropathy	48	2
Motor neuropathy	15	3
Respiratory		
Dyspnea	18	4
Hematologic		
Thrombocytopenia	32	1
Anemia	93	7
Neutropenia	88	73
Biochemical		
ALT elevation‡	18	<1
Bilirubin elevation	4	<1
Creatinine elevation	16	<1

* Toxicity was graded and reported according to expanded criteria of the National Cancer Institute of Canada Clinical Trials Group.[15,16] The percent denotes the percentage of the 231 patients who received at least one dose of the protocol treatment.
† Six percent had febrile neutropenia after the dose of vinorelbine was reduced.
‡ ALT denotes alanine aminotransferase.

P<0.001). The median recurrence-free survival was 46.7 months in the observation group and had not been reached in the chemotherapy group at the time the database was locked. The five-year recurrence-free survival rates were 61 percent (95 percent confidence interval, 54 to 68 percent) in the vinorelbine–cisplatin group and 49 percent (95 percent confidence interval, 42 to 55 percent) in the observation group (P=0.08). Use of the stratified Cox regression model showed that only chemotherapy (P<0.001) and squamous histologic features (P=0.002) were associated with significantly prolonged recurrence-free survival.

A total of 197 patients (111 in the observation group and 86 in the chemotherapy group) had died when the database was locked. Eighty-two percent of them died from recurrent lung cancer (92 in the observation group and 70 in the chemotherapy group), 5 percent from second malignant conditions (5 and 4, respectively), and 12 percent from other causes (11 and 13, respectively). Of the 11 patients in the observation group who died from other causes, 6 died from myocardial infarction, 2 from pulmonary emboli, 2 from an exacerbation of chronic obstructive pulmonary disease, and 1 from a ruptured aortic aneurysm. Of the 13 patients in the vinorelbine–cisplatin group who died from other causes, 6 died from myocardial infarction, 2 from pulmonary emboli, 1 from chronic obstructive pulmonary disease, 1 from gastrointestinal bleeding, 1 from stroke, and 2 from alcohol toxicity.

Figure 1B shows Kaplan–Meier estimates of overall survival. The median survival after chemotherapy was significantly prolonged, at 94 months (95 percent confidence interval, 73 to not reached), as compared with 73 months (95 percent confidence interval, 48 to not reached) in the observation group (hazard ratio, 0.69; 95 percent confidence interval, 0.52 to 0.91; P=0.009; P=0.04 after adjustment for interim analyses). There was an absolute survival advantage of 15 percentage points at

five years — 69 percent (95 percent confidence interval, 62 to 75 percent) in the vinorelbine–cisplatin group and 54 percent (95 percent confidence interval, 48 to 61 percent) with observation alone (P=0.03).

Subgroup analyses according to stratification factors did not show a statistically significant improvement in overall survival among patients with stage IB non–small-cell lung cancer in the chemotherapy group as compared with the observation group (P=0.79) (Fig. 1C). The median survival among patients with stage II non–small-cell lung cancer was 41 months in the observation group and 80 months in the chemotherapy group (hazard ratio, 0.59; 95 percent confidence interval, 0.42 to 0.85; P=0.004) (Fig. 1D). These findings must be considered with caution, given that no statistically significant effect of treatment according to disease stage was detected (P=0.13).

The status of *ras* mutations in the tumors is known in 450 patients (93 percent). The median survival among patients with wild-type *ras* in the observation group was 74 months and had not been reached in the group that received chemotherapy (hazard ratio, 0.69; 95 percent confidence interval, 0.49 to 0.98; P=0.03). In contrast, adjuvant chemotherapy did not seem to confer a survival advantage in patients whose tumors had *ras* mutations (hazard ratio, 0.95; 95 percent confidence interval, 0.53 to 1.71; P=0.87). However, in the interaction analysis, the effect of the status of *ras* mutations on the outcome of treatment was not statistically significant (P=0.29).

In the planned stratified Cox regression analysis, significant factors that were associated with improved survival included chemotherapy as compared with observation (hazard ratio for the difference in survival, 0.67; 95 percent confidence interval, 0.51 to 0.89; P=0.006) and squamous histologic features as compared with adenocarcinomas (P=0.005). In contrast, older age (P=0.001), male sex (P=0.03), and pneumonectomy as compared with lesser resection (P=0.02) were associated with shorter survival; *ras* mutation was not a predictor of survival.

DISCUSSION

This prospective, randomized trial documents the benefit of adjuvant vinorelbine plus cisplatin in completely resected, early-stage non–small-cell lung cancer. The overall survival advantage at five years was 15 percentage points (P=0.03), exceeding the marginal benefit (5 percentage points) observed in the British Medical Research Council meta-analysis[4] and the large IALT trial, which reported a survival advantage of 4.1 percentage points at five years (P<0.03).[5]

Three other trials of adjuvant chemotherapy for non–small-cell lung cancer undertaken during the past decade have been reported. Keller et al.[17] reported the results of the ECOG trial of adjuvant etoposide plus cisplatin and radiotherapy as compared with radiotherapy alone after resection of stage II or IIIA non–small-cell lung cancer. There was no difference between the groups in the recurrence rate or in survival, and greater toxicity was observed in the chemoradiotherapy group in this trial. Similarly, the Adjuvant Lung Project Italy (ALPI)[18] found no benefit from three cycles of mitomycin C, vindesine, and cisplatin in 1209 patients with stage I to IIIA non–small-cell lung cancer. Finally, Waller et al.[19] (of the Big Lung Trial) reported that 381 patients with non–small-cell lung cancer who were randomly assigned to various platinum-based regimens in a neoadjuvant or adjuvant setting had no benefit from treatment.

What accounts for the results of the current trial? Several important factors should be considered. The superiority of the vinorelbine–cisplatin combination has been well established in patients with advanced non–small-cell lung cancer, in whom it has been shown to provide significantly better response rates and overall survival than other regimens.[7,20-26] With the exception of IALT[5] and the Big Lung Trial,[19] in which only 27 percent and 22 percent of patients, respectively, received vinorelbine plus cisplatin, all the negative trials used older chemotherapeutic combinations with comparatively less efficacy in advanced non–small-cell lung cancer.

The CALGB protocol 9633 trial, in which another current adjuvant regimen (paclitaxel plus carboplatin) was compared with observation alone after complete resection of stage IB non–small-cell lung cancer, found a similar improvement in survival rates (an improvement of 12 percentage points at four years, vs. 15 percentage points at five years in the current trial) and a similar, significant reduction in the risk of death from recurrent lung cancer.[27] Vinorelbine plus cisplatin and paclitaxel plus carboplatin have similar efficacy in advanced non–small-cell lung cancer[22]; hence, it is not surprising that they have been found to confer similar survival benefits in the adjuvant setting.

All patients in the ECOG trial of adjuvant therapy,[17] and 31 percent and 43 percent of patients in IALT[5] and the ALPI trial,[18] respectively, received radiotherapy in addition to chemotherapy, with variable delivery of the dosage of radiotherapy between the treatment and observation groups. Radiotherapy may have had a deleterious effect on outcomes, since a meta-analysis of postoperative radiotherapy (known as PORT) showed that the risk of death increased by 21 percent with a 7 percent reduction in two-year survival with postoperative radiation.[28] Furthermore, the Medical Research Council meta-analysis of adjuvant radiotherapy with or without chemotherapy showed no benefit from chemoradiotherapy and no survival benefit from radiotherapy alone.[4] Finally, the cumulative toxic effects of chemoradiotherapy may limit the delivery of cytotoxic systemic chemotherapy and hence reduce efficacy.

Only patients with early-stage (stage IB or stage II) non–small-cell lung cancer were included in CALGB protocol 9633[27] and this trial. Previous trials included significant numbers of patients with resected stage IIIA non–small-cell lung cancer. Patients with stage IIIA disease have a high likelihood of harboring occult extrathoracic disease,

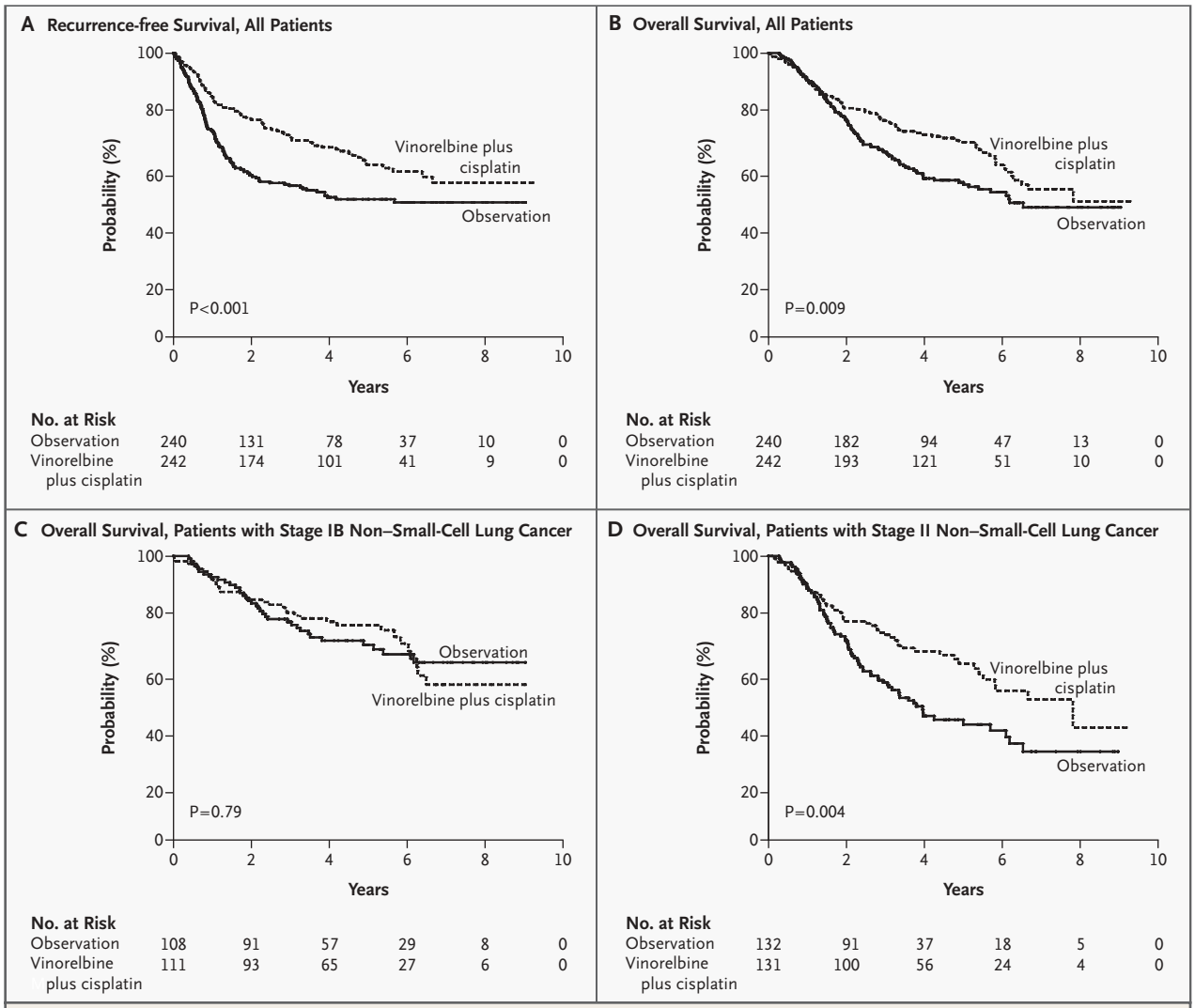

Figure 1. Kaplan–Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone.

P values are based on two-sided statistical analyses of differences between treatment groups after randomization.

are heterogeneous in terms of the extent (burden or bulk) of disease and number of nodal stations involved, frequently have a poor performance status, often require pneumonectomy, and do not tolerate chemotherapy well.[2,3,15] These factors may have contributed to the inability of these earlier trials to show a survival benefit from chemotherapy.

Subgroup analyses indicate that the survival advantage in our trial was most prominent in patients with stage II disease. We cannot explain why the benefit in patients with stage IB disease was less and did not reach statistical significance (7 percent benefit at five years, vs. 20 percent among those with stage II disease). The number of patients with stage IB disease was small, the number of events was smaller than had been anticipated when the subgroup analysis was planned, and the statistical test for stage-by-treatment interaction was not significant (P=0.13). Therefore, it is important not to place too much emphasis on this subgroup analysis.

Patients with tumors containing *ras* gene mutations have poorer survival after surgery than those without *ras* mutations, but to our knowledge, previous studies have not prospectively examined the status of *ras* genes in relation to survival or the response to adjuvant chemotherapy.[29-31] The observation that patients with *ras* mutations did not benefit from adjuvant chemotherapy, whereas those with wild-type *ras* did, requires further analysis and validation, especially because the secondary analysis for interaction terms failed to show statistically significant differences between the groups (P=0.29).

The vinorelbine–cisplatin regimen was associated with acceptable adverse event rates after reduction of the vinorelbine dose from 30 to 25 mg per square meter weekly. The rates of febrile neutropenia (7 percent) and of treatment-related death (0.8 percent) are similar to the rates of these events in other reports. Cisplatin-based regimens are associated with enhanced efficacy and toxicity as compared with carboplatin-based therapy[32,33]; yet in CALGB protocol 9633,[27] 33 percent of patients required dose reductions, and not all completed a full course of therapy. Our quality-of-life analyses showed that, despite toxicity, the decline in function- and symptom-related domains during chemotherapy in the current trial was limited and resolved rapidly (within three months after completion of therapy).[16]

This study indicates that adjuvant treatment with vinorelbine plus cisplatin can be safely administered in the outpatient setting with limited toxicity and is beneficial in non–small-cell lung cancer. We believe that a brief course of such chemotherapy should become the standard of care for patients with good performance status after complete resection of stage IB or stage II non–small-cell lung cancer.

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ORIGINAL ARTICLE

Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes

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ABSTRACT

BACKGROUND

Type 1 diabetes mellitus is a T-cell–mediated autoimmune disease that leads to a major loss of insulin-secreting beta cells. The further decline of beta-cell function after clinical onset might be prevented by treatment with CD3 monoclonal antibodies, as suggested by the results of a phase 1 study. To provide proof of this therapeutic principle at the metabolic level, we initiated a phase 2 placebo-controlled trial with a humanized antibody, an aglycosylated human IgG1 antibody directed against CD3 (ChAglyCD3).

METHODS

In a multicenter study, 80 patients with new-onset type 1 diabetes were randomly assigned to receive placebo or ChAglyCD3 for six consecutive days. Patients were followed for 18 months, during which their daily insulin needs and residual beta-cell function were assessed according to glucose-clamp–induced C-peptide release before and after the administration of glucagon.

RESULTS

At 6, 12, and 18 months, residual beta-cell function was better maintained with ChAglyCD3 than with placebo. The insulin dose increased in the placebo group but not in the ChAglyCD3 group. This effect of ChAglyCD3 was most pronounced among patients with initial residual beta-cell function at or above the 50th percentile of the 80 patients. In this subgroup, the mean insulin dose at 18 months was 0.22 IU per kilogram of body weight per day with ChAglyCD3, as compared with 0.61 IU per kilogram with placebo ($P<0.001$). In this subgroup, 12 of 16 patients who received ChAglyCD3 (75 percent) received minimal doses of insulin (≤0.25 IU per kilogram per day) as compared with none of the 21 patients who received placebo. Administration of ChAglyCD3 was associated with a moderate "flu-like" syndrome and transient symptoms of Epstein–Barr viral mononucleosis.

CONCLUSIONS

Short-term treatment with CD3 antibody preserves residual beta-cell function for at least 18 months in patients with recent-onset type 1 diabetes.

The T-cell–mediated autoimmune origin of type 1 diabetes mellitus has prompted efforts to prevent the progression of disease by targeting T lymphocytes.[1] This approach was first tested with the use of cyclosporine.[2-4] However, the benefit was lost after the withdrawal of cyclosporine, implying a need for the indefinite administration of this agent, with the attendant risks of chronic immunosuppression. Studies in nonobese diabetic mice indicated that short-term treatment with monoclonal antibodies against CD3 induced long-term remission of established diabetes[5,6] through the induction of immune tolerance that involved transforming growth factor β–dependent regulatory T cells.[7] The translation to use in the clinical setting necessitated the development of CD3 antibodies that were devoid of the toxicity that accompanies mitogenic antibodies such as muromonab-CD3 (OKT3), which produce a cytokine-related "flu-like" syndrome.[8-10] Two humanized, nonmitogenic, Fc-mutated CD3 antibodies have been available — hOKT3γ1(Ala-Ala)[11,12] and ChAglyCD3.[13-15] The first showed promise in an open-label phase 1 trial in which 12 patients who were treated with the antibody had better beta-cell function after one year and a lower insulin dosage at six months than did 12 patients who did not receive the antibody.[16] To assess the long-term metabolic efficacy of this strategy, we conducted a multicenter, randomized, phase 2 placebo-controlled trial involving the ChAglyCD3 antibody.

METHODS

PATIENT SELECTION

Patients with type 1 diabetes mellitus of recent onset were selected according to the following criteria: they were 12 to 39 years of age; had been treated with insulin for less than four weeks; had a positive result on testing for islet-cell autoantibodies, glutamic acid decarboxylase autoantibodies, or both; had a random plasma C-peptide level of more than 0.20 nmol per liter and a plasma glucose level of 180 to 250 mg per deciliter (10.0 to 13.9 mmol per liter); had had polyuria for less than six months; and had lost less than 10 percent of their body weight in the previous six months. Patients negative for Epstein–Barr virus (EBV) IgG were excluded. Details can be found in Supplementary Appendix 1 (available with the full text of this article at www.nejm.org). Written informed consent was obtained from each patient. The trial was approved by the Belgian Diabetes Registry and the ethics committee at each center.

STUDY DESIGN

Treatment with ChAglyCD3 was administered to 40 patients, and 40 patients received placebo. Patients received intensive insulin therapy (i.e., at least three injections per day) on the basis of blood glucose levels, as measured by the patient at home, to maintain levels of between 80 and 140 mg per deciliter and glycosylated hemoglobin values of less than 7.0 percent. Randomization was balanced according to center (five sites), age (less than 15 years or 15 years and older), and the presence of islet-cell antibodies.[17] A centralized minimization procedure was used. A third-party member made treatment assignments (see Supplementary Appendix 1).

The core facility of the Belgian Diabetes Registry maintained the database and performed all measurements of C peptide (results were not communicated to physicians) and of glycosylated hemoglobin (results were communicated if they were 7.0 percent or higher). Referring physicians regularly performed local glycosylated hemoglobin assays for the adjustment of insulin doses toward optimal metabolic control.

ADMINISTRATION OF ANTIBODY

ChAglyCD3 is an aglycosylated recombinant antibody (human γ1) with identical specificity to a previously described humanized aglycosylated CD3.[13-15] ChAglyCD3 was manufactured under Good Manufacturing Practice conditions[18] and formulated in phosphate-buffered saline; the formulation buffer was used as placebo.

Patients were hospitalized for the administration of ChAglyCD3 or placebo (given in an intravenous infusion over two to four hours) for six consecutive days. On the basis of a previous study protocol,[15] the first nine patients received a first dose of 24 mg, followed by infusions of 8 mg per day; four of these patients had severe headache, vomiting, or both after the first therapeutic dose. Consequently, the remaining 71 patients received six consecutive infusions of 8 mg of ChAglyCD3 or placebo per day.

EFFICACY TESTS

Residual beta-cell function was analyzed according to the measurement of C-peptide release as induced by a two-phase glucose-clamp procedure. During the first phase, before glucose infusion

(−180 to 0 minutes), euglycemia (blood glucose level, 60 to 90 mg per deciliter [3.3 to 5.0 mmol per liter]) was maintained by intravenous insulin infusion; during the second phase (0 to 146 minutes), blood glucose levels were increased and maintained at 180 to 250 mg per deciliter (10.0 to 13.9 mmol per liter); at 140 minutes, 1 mg of glucagon was injected intravenously.[19,20] Plasma samples were obtained for C-peptide measurements at 60, 90, 120, 140 and 146 minutes. The C-peptide level was measured with the use of a time-resolved fluorescence immunoassay (PerkinElmer). The area under the curve (AUC) was calculated for the induced release of C peptide before glucagon injection (at 60, 90, 120, and 140 minutes) and afterward (at 140 and 146 minutes). To compare the induced release of C peptide in both periods, we expressed the AUC value per minute for each. Every three months, the daily insulin dose, body weight, and blood glucose level as monitored by the patient were recorded, and the glycosylated hemoglobin level was measured with the use of high-performance liquid chromatography.[21]

SAFETY TESTS

During hospitalization and at each outpatient visit, patients underwent history taking, physical examination, and blood analysis as a means of monitoring for adverse events. Questionnaires were used to record acute symptoms. DNA extracted from peripheral white cells was used to screen for herpesviruses (herpes simplex virux [HSV] type 1 [HSV-1] and HSV-2, cytomegalovirus, EBV, varicella–zoster virus, and human herpesvirus 6) with the use of qualitative multiplex polymerase chain reaction (PCR) (Herpes consensus generic kit 67-090 and Herpes Hybridowell 67-050, Argene Biosoft). In 32 patients (22 in the ChAglyCD3 group and 10 in the placebo group), serial screening for EBV was also performed with the use of quantitative PCR[22]; these tests were conducted retrospectively.

IMMUNOLOGIC MONITORING

HLA-DQA and HLA-DQB genotyping and assays for islet-cell antibody and antibody against glutamic acid decarboxylase were performed at the Belgian Diabetes Registry.[23,24] Flow cytometry was used to quantify peripheral lymphocyte subsets.[8,25] Serum samples were analyzed for cytokine levels,[9] antibodies to ChAglyCD3,[26] and ChAglyCD3 concentrations.[27] EBV-specific antibodies were measured by enzyme-linked immunosorbent assay. EBV-specific CD8+ T cells were detected by immunofluorescence assay with the use of HLA class I–specific tetramers.[28,29]

STATISTICAL ANALYSIS

Data analysis was conducted according to the intention-to-treat principle and included all 80 randomized patients. The analysis compared residual beta-cell function, daily insulin dose (in IU per kilogram of body weight), glycosylated hemoglobin level, body weight, and body-mass index immediately before treatment (baseline) and at 6, 12, and 18 months. The primary end point was the change in residual beta-cell function between baseline and six months. Two-sided statistical tests were performed, with P values below 0.05 indicating significance. Comparisons of the two treatment groups were performed with the use of the t-test or Mann–Whitney test for quantitative variables and Fisher's exact test for binary variables. Comparison of the quantitative efficacy variables in the two groups was performed with the use of an analysis-of-variance model with center, treatment, and treatment-by-center interaction as factors, with the baseline value as the covariate. The Cochran–Mantel–Haenszel test was used in case there were nonnormal residuals in the model, with control for center effects. Multiple regression analysis was performed, as detailed in Supplementary Appendix 2. No adjustments were made for multiplicity.

All data shown are means ±SD. The clinical coordinator, Dr. Keymeulen, assisted by Dr. Vandemeulebroucke, the senior investigators, Drs. Pipeleers, Bach, Mathieu, and Ziegler, and the principal investigator, Dr. Chatenoud, collectively designed the protocol, vouch for the data, and wrote the manuscript. The statistician, Dr. Kaufman, was responsible for the statistical analysis. None of the coauthors involved in providing ChAglyCD3 and placebo — Dr. Hale, Ms. Rebello, Dr. Bird, Dr. Berrie, Mr. Frewin, and Dr. Waldmann, Oxford, United Kingdom — participated in data accrual or statistical analysis. Drs. Waldmann and Hale participated in the study design. Additional persons and institutions that contributed to the trial are listed in the Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of 210 patients with newly diagnosed type 1 diabetes who were screened between June 2000 and

March 2003, 39 declined to participate and 91 did not meet the inclusion criteria. Of the remaining 80 patients, 40 were randomly assigned to the ChAglyCD3 group and 40 to the placebo group. The two groups did not differ statistically in terms of clinical or laboratory characteristics (Table 1) or in the expression of susceptible or protective HLA haplotypes (data not shown).

Table 1. Characteristics of the Patients at Diagnosis, Screening, and Start of Treatment.*

Characteristic	Placebo Group (N=40)	ChAglyCD3 Group (N=40)
Demographic		
Sex (male/female)	26/14	25/15
Age (yr)	26±7	27±7
At diagnosis		
Patients with diabetic ketoacidosis (%)	19	29
Patients with polyuria and weight loss (%)	51	74
Weeks since onset of symptoms		
Median	3	4
Interquartile range	2–8	3–10
At screening		
Days since diagnosis		
Median	8	9
Interquartile range	5–16	3–18
Patients with anti–islet-cell autoantibodies (%)	75	80
Patients with glutamic acid decarboxylase antibodies (%)	90	85
At start of treatment		
Days since diagnosis		
Median	25	21
Interquartile range	19–27	18–24
Days of insulin treatment		
Median	20	19
Interquartile range	13–25	17–24
Insulin dose (IU/kg/day)	0.38±0.20	0.46±0.27
Body weight (kg)	67±12	70±15
Body-mass index†		
Median	21.1	22.1
Interquartile range	19.4–23.9	20.2–24.1

* Plus–minus values are means ±SD. Values are expressed as medians and interquartile ranges for variables for which there was a significant deviation from the normal distribution. There were no statistically significant differences between the two groups.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

EFFECTS OF TREATMENT

Before treatment, patients in the two groups had similar levels of glucose-clamp–induced C-peptide release before and after the administration of glucagon (Fig. 1A). Among patients in the placebo group, the values for C-peptide release both before and after the administration of glucagon progressively decreased over the 18 months of follow-up, reaching levels that were 33 and 37 percent lower, respectively, than at baseline (Fig. 1A). In the patients treated with ChAglyCD3, both variables increased at 6 months and returned to pretreatment levels by month 18 (Fig. 1A). The differences between treatment groups in the changes from baseline were statistically significant at all time points. Both in the absence and presence of glucagon, the patients in the ChAglyCD3 group had a net gain in C-peptide release over those in the placebo group at all time points (Table 2).

The progressive decline in residual beta-cell function in the placebo group was accompanied by a progressive rise in insulin dose, which was 50 percent higher at 18 months than at baseline (Fig. 1A). In the ChAglyCD3 group, the mean insulin dose at 18 months was 12 percent lower than at baseline (Fig. 1A). The mean differences between the groups in the change in the insulin doses from baseline were significant at all time points (Table 2). In both patient groups, there was a significant negative correlation between insulin dose and C-peptide release, both before treatment and at month 18. The Pearson's correlation coefficient was somewhat stronger at 18 months ($r=-0.60$ for placebo, $P<0.001$; $r=-0.64$ for ChAglyCD3, $P<0.001$) than before treatment ($r=-0.43$ for placebo, $P=0.006$; $r=-0.55$ for ChAglyCD3, $P<0.001$).

During the study period, the changes in mean body weight and body-mass index did not differ between the two groups (data not shown), nor did the glycosylated hemoglobin levels (Fig. 1A and Table 2), indicating that the differences in residual beta-cell function and insulin dose were not caused by inadequate insulin treatment in either group.[30] At 18 months, the glycosylated hemoglobin levels in the ChAglyCD3 group (6.9±1.3 percent) and the placebo group (6.9±1.0 percent) were almost identical; body weight was 71.8±14.5 kg and 72.3±12.9 kg, respectively.

INFLUENCE OF BETA-CELL FUNCTION AT BASELINE

In the placebo group, residual beta-cell function at baseline was the only significant factor predictive of outcome, whereas in the ChAglyCD3 group, none of the variables tested (in a stepwise, multiple linear regression model) were predictive of the response. To examine further the effect of residual beta-cell function at baseline, the patients in each group were

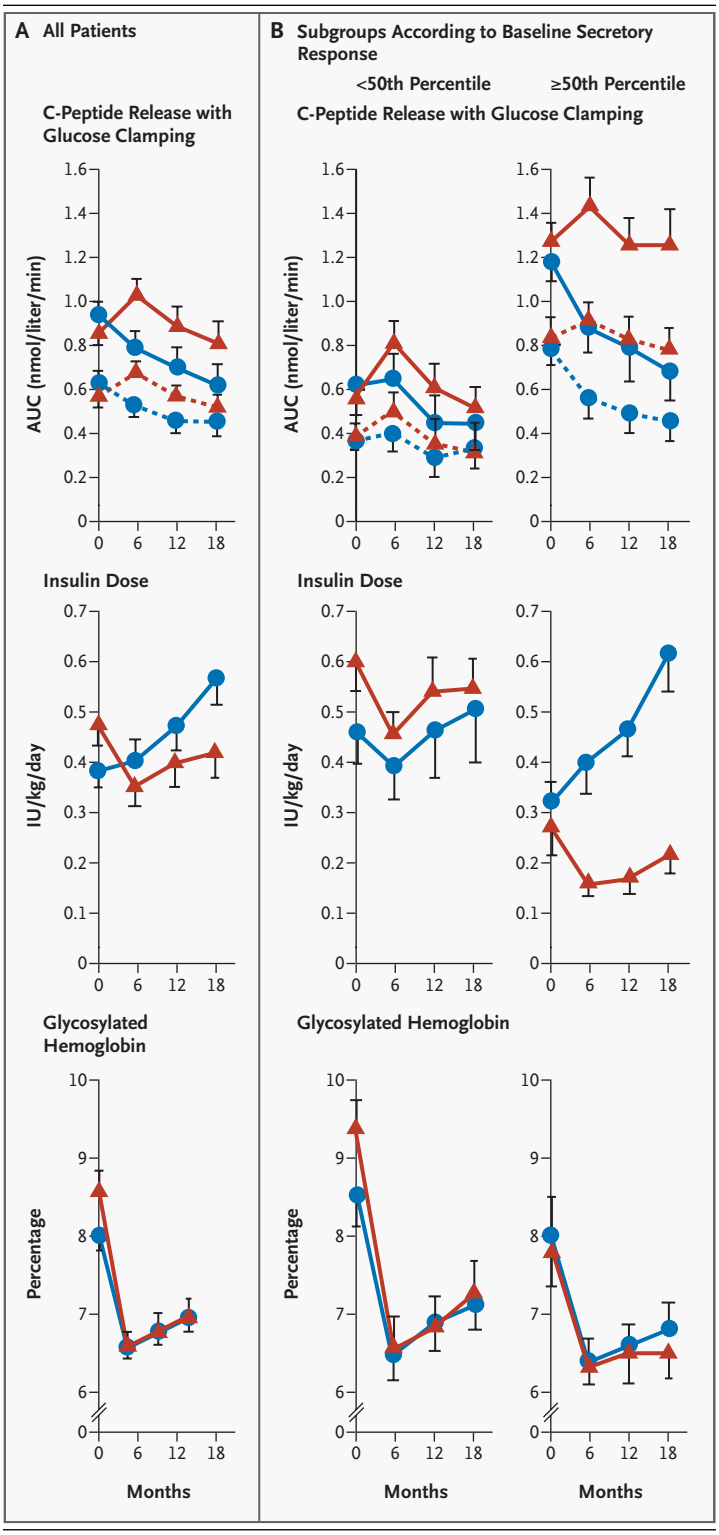

Figure 1. Efficacy Tests in the Two Study Groups.

Blue circles represent the placebo group, and red triangles the ChAglyCD3 group. Panel A shows the glucose-clamp–induced C-peptide release before glucagon injection (dashed lines) and afterward, the daily insulin needs, and the glycosylated hemoglobin levels at baseline, 6, 12, and 18 months for all patients in both groups. Panel B shows the values for these same factors according to whether the glucose-clamp–induced C-peptide release at baseline was below (left-hand side of panel) or at or above (right-hand side) the median (50th percentile) of all patients at baseline. There were 16 patients in the placebo group and 24 in the ChAglyCD3 group in whom the initial secretory response was below the 50th percentile and 24 in the placebo group and 16 in the ChAglyCD3 group in whom the response was at or above the 50th percentile. All values are means ±SE. AUC denotes area under the curve.

divided into two subgroups according to whether the initial glucose-clamp–induced C-peptide release was lower or higher than the median value of the entire population at baseline — that is, the 50th percentile, which was denoted as P50 (AUC, 0.52 nmol per liter per minute). P50 was approximately 75 percent lower than the value measured in 20 healthy, age-matched control subjects (data not shown). The demographic, clinical, and laboratory characteristics were similar in the respective subgroups (as shown in Supplementary Appendix 3).

Among the 16 patients in the placebo group in whom the initial C-peptide release was below P50, the residual beta-cell function (AUC) at 18 months remained low (values were 15 percent lower than at baseline); patients in whom the values were at or above P50 had a 41 percent decrease during this period (Fig. 1B). The mean insulin dose among patients in the placebo group who had values below P50 did not increase over the 18-month follow-up period, whereas the dose progressively increased among the 24 patients with values at or above P50, reaching values that were 1.9 times as high as those at baseline (Fig. 1B). This increase did not occur among the 16 patients treated with ChAglyCD3 in whom the initial C-peptide release was at or above P50; the residual beta-cell function was also preserved among these patients over this period (Fig. 1B).

At 18 months, the mean insulin dose among the 24 patients in the ChAglyCD3 group with baseline

Table 2. Comparison of Changes in Efficacy Tests in the Two Groups over Time.*

Efficacy Test	Difference between Groups at Baseline (CD3 minus Placebo)	Difference between Groups in Changes from Baseline					
		At Month 6	P Value	At Month 12	P Value	At Month 18	P Value
C-peptide release with glucose clamping (nmol/liter/min)							
Without glucagon	−0.12 (−0.26 to +0.03)	+0.22 (+0.06 to +0.38)	0.009	+0.22 (+0.05 to +0.39)	0.01	+0.20 (+0 to +0.38)	0.02
With glucagon	−0.20 (−0.43 to +0.02)	+0.39 (+0.12 to +0.65)	0.006	+0.40 (+0.12 to +0.69)	0.01	+0.43 (+0.13 to +0.73)	0.006
Insulin dose (IU/kg/day)	+0.07 (−0.05 to +0.19)	−0.07 (−0.19 to +0.05)	0.003	−0.12 (−0.26 to +0.03)	0.005	−0.18 (−0.35 to −0.02)	0.03
Glycosylated hemoglobin (%)	+0.77 (−0.02 to +1.56)	−0.16 (−0.72 to +0.40)	0.48	−0.17 (−0.80 to +0.47)	0.31	−0.07 (−0.77 to +0.63)	0.21

* For each group, the change in efficacy tests was calculated by subtracting the value at baseline from the value at months 6, 12, and 18. The change in each value in the placebo group was subtracted from the change in that in the ChAglyCD3 group, with the difference given here as the mean (with 95 percent confidence interval). For glucose-clamp–induced C-peptide release, positive differences indicate better results for ChAglyCD3 than for placebo. For insulin dose and glycosylated hemoglobin, negative differences indicate better results for ChAglyCD3 than for placebo.

values below P50 did not differ significantly from the dose in the comparable placebo-treated subgroup (0.54±0.30 vs. 0.51±0.33 IU per kilogram per day, respectively; P=0.73). In contrast, the mean insulin dose among the patients in the ChAglyCD3 group who had values at or above P50 at 18 months (0.22±0.11 IU per kilogram per day) was significantly lower than the dose among comparable patients in the placebo group (0.61±0.29 IU per kilogram per day, P<0.001). Glycosylated hemoglobin levels indicated that these differences were not caused by inappropriate insulin treatment (among patients with values at or above P50, 6.4±0.8 percent in the ChAglyCD3 group and 6.7±1.0 percent in the placebo group; P=0.25) (Fig. 1B). At this time point, the glycosylated hemoglobin levels in the ChAglyCD3 group were significantly lower among those with baseline C-peptide values at or above P50 than among those with values below P50 (7.2±1.4 percent, P=0.04); no difference in these levels was seen between the two subgroups within the placebo group. Analysis showed a significant treatment effect (P=0.01) as well as a significant interaction between treatment and AUC of glucose-clamp–induced C-peptide release before treatment (P=0.003).

The effect of ChAglyCD3 on insulin needs was also observed when individual patients were followed from baseline until the 18-month follow-up visit. Among the patients in the ChAglyCD3 group with values at or above P50, the percentage of patients with an insulin dosage of 0.25 IU per kilogram per day or less increased from 50 percent at baseline to 75 percent at 18 months; the percentage of patients with this dosage fell from 38 percent to 0 percent among patients in the placebo group with values at or above P50 (Fig. 2). Moreover, no patients with baseline C-peptide values at or above P50 required an insulin dosage of more than 0.75 IU per kilogram per day in the ChAglyCD3 group, whereas 30 percent of those in the placebo group required these higher dosages (Fig. 2).

IMMUNOLOGIC TESTS

Lymphocyte Counts

Treatment with ChAglyCD3 induced a transient decrease in peripheral CD2+ lymphocyte counts, which was most pronounced at day 2 and week 2, with a partial recovery occurring between these times (Fig. 3). Absolute B-lymphocyte counts (CD19+) were also transiently decreased. The recovery phase after week 2 was associated with a CD8+ T-cell lymphocytosis. This led to an inversion of the ratio of CD4+ to CD8+ lymphocytes (Fig. 3).

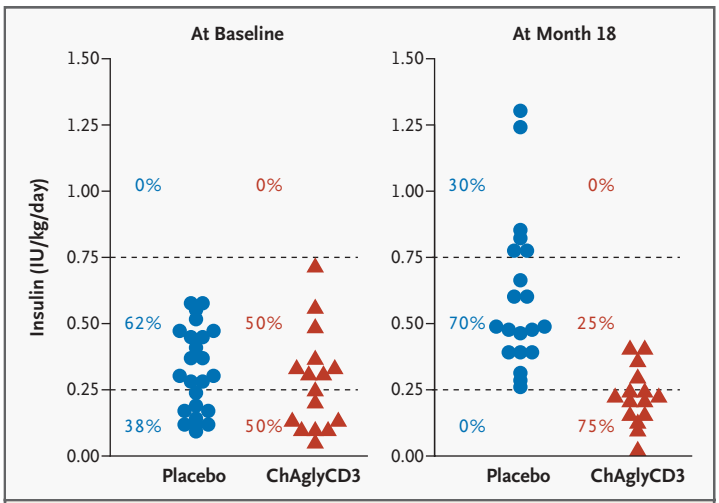

Figure 2. Comparison of Individual Insulin Doses at Baseline and 18 Months in Patients with an Initial Secretory Response at or above the 50th Percentile.
Circles represent the placebo group, and triangles the ChAglyCD3 group.

This inversion was observed in 29 of 37 patients at month 3, in 15 of 30 patients at month 6, in 10 of 33 patients at month 12, and in 9 of 31 patients at month 18 ($P<0.001$ for all, as compared with baseline).

Antigenic Modulation

During treatment with ChAglyCD3, T lymphocytes underwent antigenic modulation — that is, transient disappearance of the CD3 complex.[8,31] Thus, during treatment, most circulating T cells were CD2+CD3−CD4+ or CD2+CD3−CD8+. By day 14, T cells again expressed normal levels of CD3. Cell coating, assessed on staining with an isotype-specific antihuman IgG1 antibody, was only sporadically observed (in <1 percent of T cells) in a few patients.

Circulating ChAglyCD3 Levels

In patients who received a cumulative dose of 48 mg of ChAglyCD3, trough ChAglyCD3 concentrations increased to approximately 2 μg per milliliter (Fig. 3). By week 2, this level had decreased to less than 0.1 μg per milliliter.

Circulating Cytokine Levels

In patients who received a cumulative dose of 48 mg of ChAglyCD3, serum levels of tumor necrosis factor-α (TNF-α), interleukin-6, and interferon-γ rose after the first infusion (median peak concentrations: TNF-α, 527 pg per milliliter at one hour; interleukin-6, 1213 pg per milliliter at four hours; and interferon-γ, 4.4 IU per milliliter at four hours) and returned to normal before the third infusion. Serum interleukin-10 concentrations also increased after the first infusion (median peak concentration, 124.1 IU per milliliter at four hours) and returned to baseline levels before the third infusion. In 17 percent of patients, low interleukin-2 levels were noticed after the first or second infusion (range, 0.2 to 2.2 IU per milliliter).

Antiglobulin Responses to ChAglyCD3

Antibody responses to ChAglyCD3, including the presence of anti-idiotypic antibodies, were detected in 21 patients (53 percent), with a median time to appearance of four weeks (interquartile range, four to six weeks).

Correlation between Immunologic Tests and Treatment

No significant correlation was found between the effect of ChAglyCD3 and any of the immunologic factors tested, including the CD4:CD8 ratio after treatment, the titer of islet-cell antibodies and antibodies to glutamic acid decarboxylase before or after treatment, and HLA class II haplotypes.

ADVERSE EVENTS

All patients who received ChAglyCD3 had transient adverse events, as shown in Table 3. These included fever (see Supplementary Appendix 4), headache, gastrointestinal symptoms, arthralgia, and myalgia. The administration of ChAglyCD3 was neither delayed nor stopped in any patient because of these symptoms.

Twenty-nine of the 40 patients treated with ChAglyCD3 and 2 of the 40 treated with placebo had a rash on the palms, the trunk, or both, starting 1 week after the last infusion and lasting 5 to 18 days ($P<0.001$).

Of the 40 patients treated with ChAglyCD3, 30 had a syndrome similar to acute mononucleosis, with sore throat, fever, cervical adenopathy, or all of these, starting between day 16 and day 21 after the first infusion and resolving within 7 to 12 days ($P<0.001$ for the comparison with placebo). In 21 of 22 patients in the ChAglyCD3 group for whom samples were available, a transient increase appeared in EBV DNA copies on testing with quantitative PCR ($P<0.001$). It is important to note that all values returned to pretreatment levels by week

6 to week 12. Samples were available for testing for EBV-specific antibody in 37 patients treated with ChAglyCD3. An increase in viral-capsid-antigen–specific IgG was detected in 35 of these patients ($P<0.001$), an increase in viral-capsid-antigen–specific IgM in 13 ($P=0.04$), and an increase in early-antigen–specific IgG in 16 ($P=0.02$); all antibody levels peaked by day 28 after the first infusion. In all 16 patients treated with ChAglyCD3 for whom samples were available, an increased proportion of EBV-specific CD8+ T cells was detected with the use of tetramers that presented HLA-A2–restricted peptides, HLA-B8–restricted peptides, or both, from the lytic-cycle proteins BMLF1, BMRF1, and BZLF1.[28,29] Peak levels were observed by day 14 after the first infusion, at the time of the CD8+ T-cell lymphocytosis.

No patient had a positive result on qualitative PCR for any of the other herpes viruses for which we tested. During longer follow-up periods (24 to 57 months; median, 35 months), none of the patients treated with ChAglyCD3 had lymphoma akin to post-transplantation lymphoproliferative disease or clinical or biologic symptoms related to a syndrome of this type. Patients in both groups will continue to be monitored for possible late-onset side effects of the antibody treatment. Few episodes of severe hypoglycemia were detected, with no difference between patients receiving placebo and those receiving ChAglyCD3 (two episodes over 18 months).

DISCUSSION

This study documents that further loss of residual beta-cell function occurs during the 18 months after a diagnosis of type 1 diabetes mellitus in patients 12 to 39 years of age. Beta-cell function was assessed through the release of C peptide during prolonged glucose stimulation, first in the absence of an exogenous glucagon stimulus and then in the presence of this stimulus. Glucagon significantly increased the release of C peptide (by 46 to 65 percent) at all time points, indicating that beta cells maintained a secretory response to glucagon despite the diabetic state and a prior two-hour exposure to frank hyperglycemia. Both indexes of beta-cell function progressively decreased after diagnosis, with an average reduction of 35 percent after 18 months. This reduction was accompanied by a 50 percent rise in mean daily insulin needs.

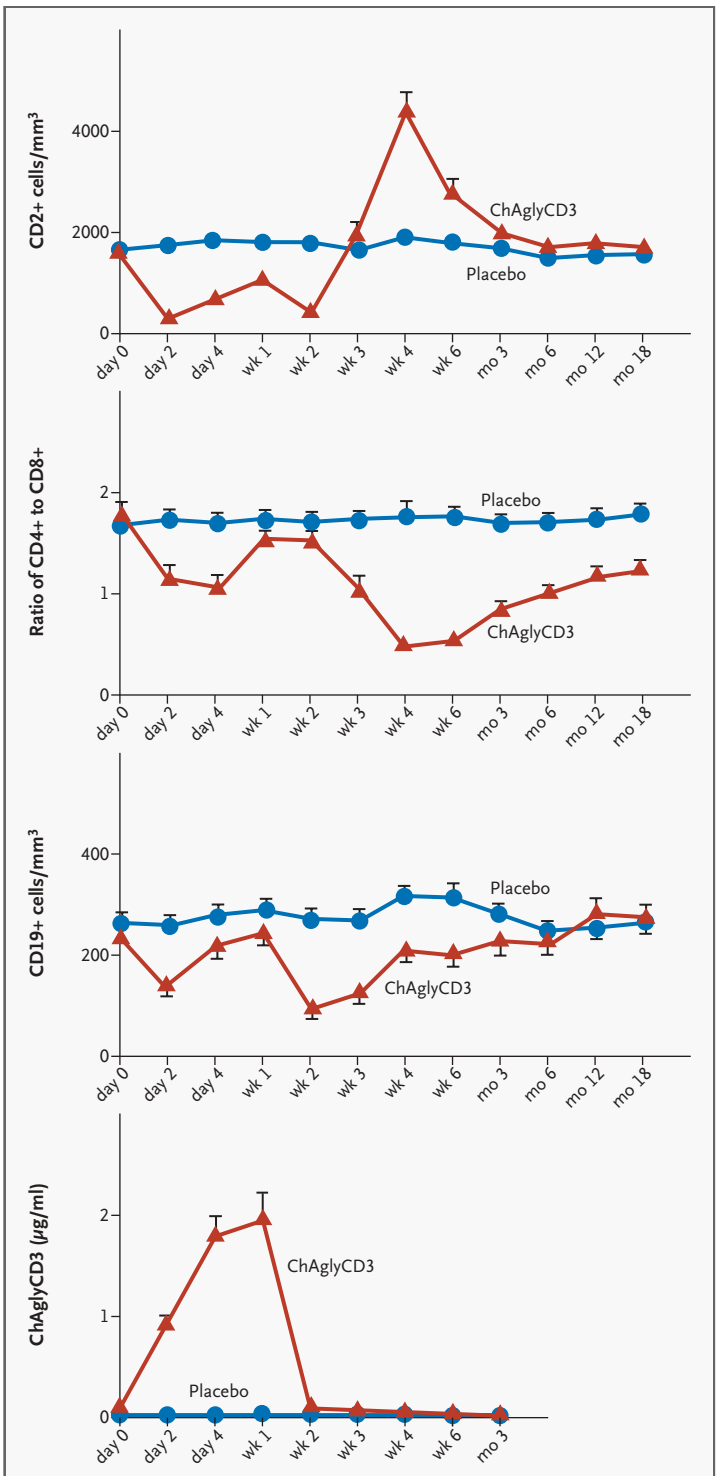

Figure 3. Immunologic Tests among Patients in the Two Groups.
All values are means ±SE. Circles represent the placebo group, and triangles the ChAglyCD3 group.

Table 3. Adverse Events among Patients in the Two Groups.*

Sign or Symptom	ChAglyCD3 (N=40)	Placebo (N=40)	P Value
	no. of patients		
During treatment			
Fever (>38.0°C)	38	1	<0.001
Headache	40	14	<0.001
Gastrointestinal symptoms	39	7	<0.001
Arthralgia	40	2	<0.001
Myalgia	35	8	<0.001
Onset at day 11–15			
Rash	29	2	<0.001
Onset at day 16–21			
Acute mononucleosis-like syndrome			
Sore throat	30	3	<0.001
Fever	13	1	0.001
Cervical adenopathy	10	3	0.07

* The cumulative dose of ChAglyCD3 was 48 mg in 35 patients, 64 mg in 4 patients, and 24 mg in 1 patient (treatment was discontinued after three 8-mg doses in this patient because of catheter sepsis).

The results of this trial indicate that short-term treatment with ChAglyCD3 ameliorates this reduction in residual beta-cell function. No rise in the daily insulin dose was observed, indicating that the short-term antibody treatment exerts a durable effect for at least 18 months. It is interesting to note that the protection induced by ChAglyCD3 was much less pronounced in patients with baseline residual beta-cell function that was lower than that for the 50th percentile of the study population; the insulin dose in these patients increased only marginally over 18 months if they were in the placebo group, and ChAglyCD3 treatment did not lead to a lower mean insulin dose. Patients with higher residual function at baseline (P50 or more of the study population) required less insulin initially, but in those receiving placebo, insulin requirements almost doubled during the first 18 months. This increase in the insulin requirement was associated with a 47 percent reduction in residual beta-cell function, indicating that patients with higher residual beta-cell function at diagnosis lose an important part of this function during subsequent months, probably as the result of a further decline in beta-cell mass.

Treatment with ChAglyCD3 prevented this loss in residual beta-cell function, and consequently, daily insulin needs remained stable over the 18-month follow-up period. At month 18, the majority of patients in the ChAglyCD3 group who had higher beta-cell function at baseline needed a daily insulin dose of 0.25 IU per kilogram per day or less, whereas this low dose was not sufficient to maintain glucose control in any of the patients in the placebo group. This subgroup also had the lowest glycosylated hemoglobin levels — 6.4 percent at month 18, a surrogate for good metabolic control. Thus, treatment with ChAglyCD3 confers a metabolic benefit that is most apparent in patients with higher residual beta-cell function. This effect might be explained by the administration of the antibody at an earlier stage of the disease. Our data extend the findings of an open-label trial with another humanized anti-CD3 antibody, hOKT3γ1(Ala-Ala), which showed positive results at 12 months.[16] Entry criteria in the present trial were more stringent, with a clear definition of metabolic state, which perhaps selected for a subgroup of patients who would respond to antibody treatment.

The therapeutic potential of ChAglyCD3 will depend on its safety. Symptoms observed after the first infusions were compatible with transient cytokine release. The transient rashes were similar to those previously described.[16] Clinical symptoms of infectious mononucleosis were observed in 75 percent of patients and coincided with transiently positive results on EBV-specific quantitative PCR. It is important to note that the values for EBV-specific PCR returned to baseline levels in all patients within 5 to 10 weeks after treatment; this was associated with the development of an antibody response and a CD8+ T-cell response specific for EBV antigens of the lytic cycle. This pattern differs from that observed in cases of EBV reactivation in patients with chronic immunosuppression, potentially leading to post-transplantation lymphoproliferative disease. Although a return to baseline values occurred in all patients who received ChAglyCD3, long-term follow-up will be important.

In conclusion, this placebo-controlled study demonstrates a sustained metabolic benefit from a short course of ChAglyCD3 in patients with recent-onset type 1 diabetes. The treatment appears to preserve residual beta-cell function, thereby preventing an increase in exogenous-insulin needs for at least 18 months. This effect appears to be most pronounced in persons with a higher initial residual beta-cell function. Treatment with ChAglyCD3 was

accompanied by significant, but seemingly transient, side effects, including fever after the start of infusions and rash and acute mononucleosis-like syndrome after the end of treatment.

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APPENDIX

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ORIGINAL ARTICLE

Peginterferon Alfa-2b and Ribavirin for 12 vs. 24 Weeks in HCV Genotype 2 or 3

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ABSTRACT

BACKGROUND

We hypothesized that in patients with hepatitis C virus (HCV) genotype 2 or 3 in whom HCV RNA is not detectable after 4 weeks of therapy, 12 weeks of treatment is as effective as 24 weeks.

METHODS

A total of 283 patients were randomly assigned to a standard 24-week regimen of peginterferon alfa-2b at a dose of 1.0 μg per kilogram weekly plus ribavirin at a dose of 1000 mg or 1200 mg daily, on the basis of body weight. Of these, 70 patients were assigned to the 24-week regimen (standard-duration group) and 213 patients to a variable regimen (variable-duration group) of 12 or 24 weeks, depending on whether tests for HCV RNA were negative or positive at week 4. The primary end point was HCV that was not detectable by polymerase-chain-reaction (PCR) assay 24 weeks after the completion of therapy.

RESULTS

In the standard-duration group, 45 (64 percent) patients had HCV that was not detectable by PCR assay at week 4, as compared with 133 (62 percent) in the variable-duration group (difference [the rate in the standard-duration group minus that in the variable-duration group], 2 percent; 95 percent confidence interval, −11 to 15 percent). Fifty-three patients (76 percent) in the standard-duration group and 164 patients (77 percent) in the variable-duration group had a sustained virologic response (difference, −1 percent; 95 percent confidence interval, −13 to 10 percent). Fewer patients in the variable-duration group receiving the 12-week regimen had adverse events and withdrew than in the group receiving the 24-week regimen (P=0.045). The rate of relapse (defined as HCV not detectable at the end of treatment but detectable at the end of follow-up) was 3.6 percent in the standard-duration group and 8.9 percent in the variable-duration group (P=0.16). Overall, the rate of sustained virologic response was 80 percent among patients with HCV genotype 2 and 66 percent among those with genotype 3 (P<0.001).

CONCLUSIONS

A shorter course of therapy over 12 weeks with peginterferon alfa-2b and ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a response to treatment at 4 weeks.

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In most patients with chronic hepatitis C virus (HCV) genotype 2 or 3 infection, therapy with pegylated interferon and ribavirin administered for a period of 24 or 48 weeks ensures a sustained virologic response.[1-3] Although these schedules are effective, side effects increase with the length of treatment.[4] Furthermore, there have been isolated reports of patients who, with therapy withdrawn after only 8 to 12 weeks, have a response.[5] Therefore, current recommendations may lead to overtreatment of some patients with chronic HCV infection.

Experimental data substantiate these observations. On the initiation of interferon therapy, there is a rapid decline in viral load, reflecting the efficiency of interferon-dependent inhibition of the production of the virus, its release, or both. This rapid decline is followed by a slower one that is dependent on the rate of death of infected cells and that is estimated to vary from 1.7 days to more than 70 days.[6] Both the effectiveness of interferon in blocking production of the virus in the first phase of decline and the rate of decline in the second phase differ in patients with HCV genotype 1 and in those with genotype 2 or 3, with a decline eight times faster in patients with genotypes other than 1.[7,8] This difference suggests that patients with HCV genotype 2 or 3 infection need shorter courses of therapy than the regimens currently recommended.[9,10] Changes in viremia levels over the first weeks of therapy correlate with the likelihood of the eradication of HCV, and undetectable viral levels at week 12 are predictive of a response after 48 weeks of therapy.[6,8,11] Moreover, the early viral response can vary in patients with HCV genotype 1 and those with genotypes other than 1, and this variation is an independent predictor of sustained virologic response.[12-15]

Data on viral kinetics have led to the hypothesis that in patients with HCV genotype 2 or 3 in whom HCV RNA is not detectable after 4 weeks of therapy, 12 weeks of treatment may be as effective as the recommended course of 24 weeks.

METHODS

STUDY DESIGN

We conducted a randomized trial in patients with HCV genotype 2 or 3 comparing the standard 24-week regimen with a variable-duration regimen. Patients with a virologic response at 4 weeks received treatment for 12 weeks and those without a virologic response at 4 weeks received treatment for 24 weeks. The primary measure of efficacy was a sustained virologic response, defined as HCV RNA that was not detectable in the serum 24 weeks after treatment was stopped. This open-label trial was conducted in 12 centers in Italy as an investigator-sponsored study without financial support from industry. The study was approved by a central ethics committee and was conducted according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. Eligible patients were 18 to 70 years of age; had antibodies to HCV, infection with genotype 2 or 3, and abnormal alanine aminotransferase levels; and had not received therapy. All patients provided written, informed consent. Enrollment started in June 2002, and the trial ended in January 2004. Exclusion criteria included a leukocyte count lower than 3000 per cubic millimeter, a platelet count lower than 80,000 per cubic millimeter, a hemoglobin level lower than 12 g per deciliter for women and lower than 13 g per deciliter for men, infection with the human immunodeficiency virus, alcohol intake greater than 20 g daily, and the presence of drug abuse, chronic disease, psychiatric disease, autoimmune disease, or pregnancy and lactation.

Patients were randomly assigned in a 1:3 ratio to receive peginterferon alfa-2b (PEG-Intron, Schering) at a dose of 1.0 μg per kilogram of body weight weekly plus oral ribavirin (Rebetol, Schering) at a dose of 1000 mg (for those with a weight of <75 kg) or 1200 mg (for those with a weight of ≥75 kg) daily, administered either for the standard period of 24 weeks (in the control standard-duration group of 70 patients) or for a variable duration (in the variable-duration group of 213 patients), according to HCV RNA status at week 4 (Fig. 1). In the variable-duration group, 133 patients with an early response (those in whom HCV RNA was not detectable at week 4) stopped therapy at week 12, whereas 80 patients with detectable levels of virus at week 4 received therapy until week 24. The treatment of patients with detectable HCV RNA at week 4 was similar, whether they were in the standard-duration group or the variable-duration group. Participants were assessed on an outpatient basis at weeks 4, 8, 12, and 24 during treatment and at week 24 after treatment ended.

VIROLOGIC AND HISTOLOGIC EVALUATION

At each participating center, blood samples were collected at weeks 4, 12, and 24 during treatment and at week 24 of follow-up, and hematologic and virologic testing was performed within 10 days af-

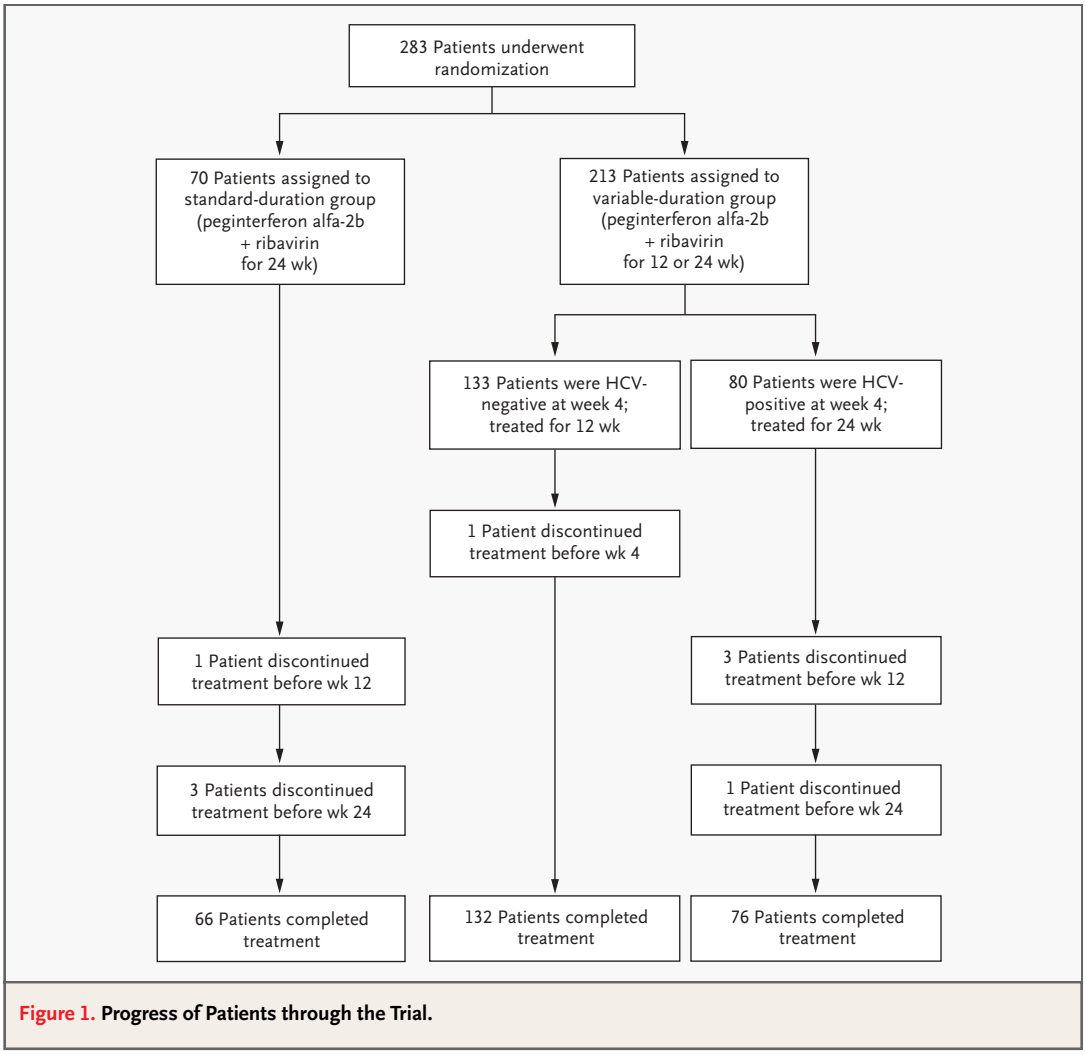

Figure 1. Progress of Patients through the Trial.

ter collection on samples stored at −20°C (−4° F). Serum levels of HCV RNA were evaluated qualitatively at each time point by polymerase-chain-reaction (PCR) assay (Amplicor HCV test, version 2.0, Roche Diagnostics) and quantitatively at baseline (Cobas Monitor test, version 2.0, Roche Diagnostics). HCV genotyping was performed with the use of a hybridization technique (Innolipa HCV, Innogenetics). A total of 266 patients underwent liver biopsy before therapy, and histologic evaluation was carried out according to the Scheuer classification system.[16] Steatosis was graded as mild (<30 percent), moderate (30 to 60 percent), or severe (>60 percent), according to the percentage of hepatocytes with macrovesicular steatosis. Treatment was started within one or two months after liver biopsy.

SAFETY ANALYSIS

Adverse events were graded as mild, moderate, or severe. When severe events other than anemia occurred, the dose of peginterferon alfa-2b was decreased by 50 percent and the dose of ribavirin was lowered to 800 mg daily; full doses were resumed when the event abated. If the event persisted, both drugs were discontinued. In the presence of anemia, the dose of ribavirin was lowered to 800 mg per day if hemoglobin levels were lower than 9.5 g per deciliter, and ribavirin was discontinued if the concentrations fell below 8.0 mg per deciliter.

STATISTICAL ANALYSIS

The study was designed as a noninferiority trial comparing the standard-duration and variable-duration strategies. It was recognized that data on

the standard-duration group would provide little new information and that experience gained with the new variable-treatment schedule would be advantageous. Therefore, for randomization a 3:1 ratio was considered, with approximately 210 subjects to be assigned to the variable-duration group and 70 to the standard-duration group. Randomization was performed centrally, without stratification according to genotype and with the use of a permuted-block method, in which each block included 28 patients, to ensure the 3:1 proportion of subjects in the two treatment groups. These sample sizes would provide the study with 80 percent power to rule out a difference of at least 12.5 percent, assuming an 80 percent rate of sustained virologic response in each group and with the use of a one-sided 95 percent confidence interval. If a rate of response of 80 percent was observed in the two treatment groups, a difference of at least 9.1 percent would be ruled out. Given the very high response rates attained by treatment of the standard duration and the considerable advantage of a shorter treatment as offered by the variable-duration regimen, a noninferiority margin of 12.5 percent was considered to be acceptable in this setting.

Patients who dropped out of the trial were classified as not having a virologic response. Patients with relapse were considered to be those with tests that were negative for HCV RNA at the end of therapy but positive at the end of follow-up. No interim analyses were performed, and the analyses included all randomized subjects for whom there were outcome data. Differences in baseline characteristics between the two groups were assessed with the use of the chi-square test with Yates's correction for discrete variables and the two-sided t-test with confidence intervals set at 95 percent. The primary comparison was between patients in the standard-duration group treated for 24 weeks and those in the variable-duration group treated for either 12 or 24 weeks. Patients assigned to the standard-duration group were subdivided at the end of week 4 into those in whom HCV RNA was not detectable (early response) and those with detectable levels of HCV RNA (no early response).

A prediction model for sustained virologic response based on undetectable HCV RNA levels at week 4 was developed that included HCV genotype, HCV RNA levels, body-mass index, alanine aminotransferase values, and the presence or absence of bridging fibrosis or cirrhosis. Stepwise logistic-regression analysis was performed to compare P values and odds ratios for the effect of prognostic factors and length of treatment on the response. At the start of the analysis, all considered variables were included in the model. A backward procedure was then applied, and a maximum-likelihood method was used for entering or removing terms (SPSS for Windows, version 11.0). All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

Patients in the two treatment groups were well matched for baseline characteristics (Table 1). The ratio of those with HCV genotype 2 or 3 was approximately 3 to 1 in each group at the start of the trial.

RESPONSE RATES ACCORDING TO THERAPY AND GENOTYPE

In the standard-duration group, 45 of 70 patients (64 percent) had undetectable levels of HCV RNA at week 4, as compared with 133 of 213 patients (62 percent) in the variable-duration group (difference [the rate in the standard-duration group minus that in the variable-duration group], 2 percent; 95 percent confidence interval, −11 to 15 percent). Twenty-four weeks after completing treatment, 53 patients (76 percent) in the standard-duration group and 164 patients (77 percent) in the variable-duration group had a sustained virologic response (difference, −1 percent; 95 percent confidence interval, −13 to 10 percent). Since our prespecified margin was 12 percent and the upper limit of the confidence interval for the standard-duration group as compared with the variable-duration group was 10 percent, the criterion for noninferiority was satisfied.

In the standard-duration group (45 patients) and in the variable-duration group treated for 12 weeks (133 patients), 41 patients (91 percent) and 113 patients (85 percent), respectively, had a sustained virologic response, a difference of −6 percent (95 percent confidence interval, −16 to 4 percent). Twelve of 25 patients (48 percent) in the standard-duration group without an early response and 51 of 80 patients (64 percent) in the variable-duration group treated for 24 weeks were HCV RNA-negative 24 weeks after the completion of treatment, a difference of −16 percent (95 percent confidence interval, −6 to 38 percent).

Overall, 171 of 213 patients with HCV genotype 2 (80 percent) and 46 of 70 patients with HCV geno-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Standard-Duration Group (N=70)	Variable-Duration Group (N=213)	P Value
Age — yr	49.7±12.1	46.6±12.2	0.71
Male sex — no. (%)	39 (56)	119 (56)	0.50
Route of transmission — no. (%)			
Intravenous	13 (19)	41 (19)	0.92
Parenteral	15 (21)	49 (23)	0.77
Unknown	42 (60)	123 (58)	0.71
Body-mass index†			
Mean	26.0±3.2	25.7±3.7	0.06
≥27 — no. (%)	29 (41)	79 (37)	0.51
Body weight — kg			
Mean	69.5±10.3	69.4±9.7	0.31
≥75 kg — no. (%)	20 (29)	66 (31)	0.71
Alanine aminotransferase — U/liter‡			
Mean	109±10	110±5	0.82
>120 U/liter — no. (%)	17 (24)	72 (34)	0.11
HCV genotype — no. (%)			
2	53 (76)	160 (75)	0.53
3	17 (24)	53 (25)	0.50
HCV RNA — IU/ml			
Mean	809,000±960,000	1,019,000±1,430,000	0.20
>800,000 IU/ml — no. (%)	46 (66)	137 (64)	0.50
Moderate or severe steatosis — no. (%)	25 (36)	65 (31)	0.64
Liver fibrosis, stage ≥3 — no. (%)§	16 (23)	35 (16)	0.36

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The upper limit of normal for alanine aminotransferase was 40 U per liter.
§ Liver histology was unavailable for 17 patients, 2 in the standard-duration group and 15 in the variable-duration group.

type 3 (66 percent) had a sustained virologic response, a difference of 14 percent (95 percent confidence interval, 2 to 27 percent; P<0.001). There was no significant difference in the numbers of patients with genotype 2 or 3 in whom HCV RNA was undetectable by week 4: 137 patients with HCV genotype 2 (64 percent) and 41 with genotype 3 (59 percent) (P=0.47). Among patients with HCV genotype 2, the rate of sustained virologic response was 76 percent in the standard-duration group and 82 percent in the variable-duration group (Table 2). Response rates among patients with HCV genotype 2 with undetectable HCV on PCR assay at the end of follow-up were 89 percent in the standard-duration group and 87 percent in the variable-duration group (difference, −1.3 percent; 95 percent confidence interval, −11 to 14 percent). When patients with HCV genotype 2 and an early response were considered in relation to length of treatment, the response rates were 87 percent in the variable-duration group treated for 12 weeks and 89 percent in the standard-duration group (P=0.90); continued treatment in patients with viremia at week 4 resulted in response rates of 50 percent among those in the standard-duration group without an early response and 72 percent in the variable-duration group treated for 24 weeks (P=0.13). In patients with HCV genotype 3 and an early response, sustained virologic response rates were 77 percent among those in the variable-duration group treated for 12 weeks and 100 percent among those in the standard-duration group with an early response (P=0.24), whereas among patients with viremia at week 4, the response rates were 43 percent among those in the standard-duration group without an early response and 41 percent among those in the variable-duration group treated for 24 weeks (P=0.68).

Table 2. Patients Who Were HCV RNA–Negative at the End of Treatment and Follow-up, According to HCV Genotype and Regimen.*

Patients and Point in Study	Standard-Duration Regimen (24 Weeks)						Variable-Duration Regimen (12 or 24 Weeks)					
	All Patients		Negative at Week 4 (Early Response)		Positive at Week 4 (No Early Response)		All Patients		Negative at Week 4 (12-Week Treatment)		Positive at Week 4 (24-Week Treatment)	
	no.	% *(95% CI)*	*no.*	% *(95% CI)*	*no.*	% *(95% CI)*	*no.*	% *(95% CI)*	*no.*	% *(95% CI)*	*no.*	% *(95% CI)*
All patients	70		45	64.3	25	35.7	213		133	62.4	80	37.6
End of treatment	55	79 (68–88)	42	93 (86–100)	13	52 (32–71)	180	85 (80–89)	126	95 (91–96)	54	68 (56–77)
End of follow-up	53	76 (66–86)	41	91 (83–99)	12	48 (28–67)	164	77 (71–83)	113	85 (79–91)	51	64 (53–74)
HCV genotype 2	53		35		18		160		102		58	
End of treatment	42	79 (68–90)	32	91 (82–100)	10	56 (32–78)	143	89 (65–94)	98	96 (92–99)	45	78 (67–88)
End of follow-up	40	76 (64–87)	31	89 (78–99)	9	50 (27–73)	131	82 (76–88)	89	87 (81–91)	42	72 (61–84)
HCV genotype 3	17		10		7		53		31		22	
End of treatment	13	76 (59–97)	10	100	3	43 (6–79)	37	70 (57–82)	28	90 (80–100)	9	41 (30–61)
End of follow-up	13	76 (56–97)	10	100	3	43 (6–79)	33	62 (49–75)	24	77 (63–92)	9	41 (30–61)

* CI denotes confidence interval.

SAFETY

In the variable-duration group, adverse events (depression and thyroid dysfunction) occurred in 8 patients treated for 12 weeks (6 percent) and in 19 treated for 24 weeks (13 percent) (P=0.056). In the variable-duration group, fewer patients (one) treated for 12 weeks reported side effects that required withdrawal from the study therapy than those treated for 24 weeks (eight patients) (P=0.045) (Fig. 1). Hemoglobin levels were reduced to less than 9.5 g per deciliter in 6 patients (4 percent) in the variable-duration group treated for 12 weeks and in 14 patients (9 percent) treated for 24 weeks (P=0.17). Anemia (defined as a hemoglobin level of <12 g per deciliter in women or <13 g per deciliter in men) and neutrophil counts of less than 1000 per cubic millimeter required a reduction in the dose of the study drug in 7 patients treated for 12 weeks (5 percent) and 18 patients treated for 24 weeks (12 percent).

PREDICTORS OF RAPID RESPONSE

In the univariate analyses, low levels of viremia were significantly associated with an early response to treatment (P=0.049), and high alanine aminotransferase levels approached significance (P=0.06) (Table 3). In the multivariate analysis, no factors remained statistically significant (Table 3).

RELAPSE RATES

Among patients who were HCV-negative at the end of treatment, 2 of 55 (3.6 percent) in the standard-duration group and 16 of 180 (8.9 percent) in the variable-duration group had detectable HCV RNA 24 weeks after the end of follow-up (P=0.16). Among patients with relapse in 24 weeks of follow-up who were HCV-negative at the end of treatment, 1 of 42 was in the standard-duration group with an early response (2 percent), 1 of 13 was in the standard-duration group without an early response (8 percent), 13 of 126 were in the variable-duration group treated for 12 weeks (10 percent), and 3 of 54 were in the variable-duration group treated for 24 weeks (6 percent). The rate of relapse among patients in the variable-duration group treated for 12 weeks was not different from that among patients in the standard-duration group with an early response (P=0.19). All patients with relapse in the variable-duration group who were treated for 12 weeks were offered retreatment with the same dose of peginterferon alfa-2b and ribavirin for an additional 24 weeks. Most of these patients (10 of 13) agreed to be retreated, and 9 had a sustained virologic response. No baseline characteristic was associated with relapse among the 133 patients in the variable-duration group treated for 12 weeks who had an initial response; however, there was a trend toward a higher rate of relapse among patients with alanine aminotransferase levels no more than three times the upper limit of normal than among those with levels more than three times the upper limit of normal (14 percent vs. 2 percent, P=0.06) (Table 4).

Table 3. Factors Associated with Early Virologic Response at 4 Weeks.*

Factor	Patients with Early Response (N=178)	Patients with Viremia (N=105)	P Value	Odds Ratio (95% CI)	P Value
			Univariate Analysis		Multivariate Analysis
	number (percent)				
Age <40 yr	52 (29)	37 (35)	0.42	0.87 (0.48–1.56)	0.64
Female sex	82 (46)	43 (41)	0.63	1.08 (0.63–1.85)	0.75
Body-mass index <27	108 (61)	69 (66)	0.61	0.92 (0.53–1.59)	0.76
Alanine aminotransferase >3× upper limit of normal	127 (71)	67 (64)	0.06	1.22 (0.69–2.15)	0.48
HCV RNA <800,000 UI/ml	121 (68)	62 (59)	0.049	1.56 (0.92–2.64)	0.09
HCV genotype					
2	137 (77)	75 (71)	0.37	0.84 (0.43–1.65)	0.62
3	41 (23)	30 (29)	0.37	0.84 (0.43–1.65)	0.62
Mild steatosis	114 (64)	64 (61)	0.89	1.01 (0.67–1.53)	0.94
Fibrosis, stage <3	135 (76)†	84 (80)‡	0.39	1.33 (0.68–2.16)	0.39

* Patients with early response were in the standard-duration group and those in the variable-duration group treated for 12 weeks. Patients with viremia were in the standard-duration group and those in the variable-duration group treated for 24 weeks. CI denotes confidence interval.
† Of 178 patients, 165 had a liver biopsy.
‡ Of 105 patients, 101 had a liver biopsy.

DISCUSSION

In patients with HCV genotype 2 or 3, a strategy of variable-duration treatment with peginterferon alfa-2b and ribavirin (so that patients with a response at week 4 were treated for 12 weeks rather than 24 weeks) achieved rates of sustained virologic response similar to those achieved with the standard treatment (24 weeks). Patients treated for 12 weeks were spared the expense and inconvenience of extended treatment and still had a high response rate. The shorter regimen was associated with fewer side effects and, consequently, less frequent withdrawals from therapy. Moreover, patients assigned to 12 weeks of treatment were less likely to require a reduction in the dose of peginterferon alfa-2b or of ribavirin. The proportion of patients with relapse was higher among those treated for 12 weeks than those treated for the standard 24 weeks. However, 90 percent of patients with a relapse after 12 weeks of treatment had a response after an additional 24-week course of therapy. Therefore, even taking into consideration the rate of relapse, treatment for 12 weeks rather than 24 weeks appears to be appropriate for patients with an early response.

These results are consistent with the results of an uncontrolled Norwegian study in which 85 of 95 patients (89 percent) with HCV genotype 2 or 3 had a response 14 weeks after peginterferon alfa-2b and ribavirin therapy was initiated.[17] That investigation and our study differed in the weekly dose of peginterferon alfa-2b: the Norwegian study administered 1.5 μg per kilogram of body weight, whereas the current trial used 1.0 μg per kilogram. In another study, by Manns et al., the benefit of a high-dose regimen was most apparent in patients with HCV genotype 1 infection, whereas those with genotype 2 or 3 achieved similar response rates with high- and low-dose peginterferon alfa-2b regimens.[2] However, because modification of the dose of ribavirin in patients with anemia was less stringent in our trial than in other trials,[2,4,18] the overall dose of ribavirin received by our patients may have been higher than in previous trials. Furthermore, preliminary results have been presented from a randomized study comparing 16 weeks with 24 weeks of combination therapy with peginterferon alfa-2a plus ribavirin in patients infected with HCV genotype 2 or 3, in which combination therapy for 16 or 24 weeks achieved similar rates of sustained virologic response among patients with an early response at week 4.[19]

Table 4. Association between Baseline Characteristics and Rate of Relapse among 133 Patients in the Variable-Duration Group with Early Response Assigned to 12 Weeks of Treatment.

Characteristic	No. of Patients	No. with Relapse (%)	P Value
All patients	133	13 (10)	
Age			0.57
<40 yr	85	9 (11)	
≥40 yr	48	4 (8)	
Sex			0.42
Male	68	8 (12)	
Female	65	5 (8)	
Body-mass index			0.62
≥27	50	4 (8)	
<27	83	9 (11)	
Alanine aminotransferase			0.06
<3× upper limit of normal	87	12 (14)	
≥3× upper limit of normal	46	1 (2)	
HCV RNA			0.38
<800,000 IU/ml	45	3 (7)	
≥800,000 IU/ml	88	10 (11)	
HCV genotype			0.50
2	102	9 (9)	
3	31	4 (13)	
Steatosis			0.84
Moderate or severe	39	4 (10)	
Absent or mild	94	9 (10)	
Fibrosis, stage*			0.84
≥3	18	2 (11)	
<3	114	11 (10)	

* One patient declined to undergo the biopsy.

No quantitative estimation of HCV viremia was planned in the current study, because we defined an early virologic response as a negative test for HCV RNA after 4 weeks of treatment. So far, quantitative evaluation of HCV RNA has been used as a criterion for stopping therapy in patients with HCV genotype 1 without early virologic response, but this criterion has not been used to tailor the length of therapy. It has recently been reported that antiviral therapy is more beneficial in patients with HCV genotype 2 than those with genotype 3,[18] and data from our trial support these findings. Overall, response rates were 80 percent and 66 percent, respectively, in patients with these two genotypes (P<0.001). However, our findings suggest that stopping therapy after 12 weeks in patients with a response at 4 weeks is appropriate for patients with either genotype, because the rates of sustained virologic response were similar in patients with genotype 2 or 3 who had an early response and who were treated for 12 or 24 weeks. In keeping with a preliminary report from the DITTO study,[13] after early viral clearance has been obtained, the role of genotype appears to be relatively small. From the current trial, it is evident that prolonging treatment in patients with detectable HCV RNA at week 4 of therapy achieved higher rates of response in those with genotype 2 than those with genotype 3; among patients who did not have an early response and were treated for 24 weeks, the rate of sustained virologic response was higher among those with HCV genotype 2 than among those with genotype 3.

In conclusion, our findings suggest that patients with HCV genotype 2 or 3 infection who have undetectable HCV RNA after 4 weeks of treatment with peginterferon alfa-2b and ribavirin achieve high response rates with 12 weeks of therapy and do not require 24 weeks of treatment. Tailoring treatment so that those with an early response are given a shorter course may make therapy more appealing to patients, without adversely affecting outcomes.

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CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.

REVIEW ARTICLE

CURRENT CONCEPTS

Vertebrobasilar Disease

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Eighty percent of strokes are ischemic. Twenty percent of ischemic events involve tissue supplied by the posterior (vertebrobasilar) circulation (Fig. 1). The paralysis of vertebrobasilar stroke can be devastating, and some forms have high rates of death.[1] Many cases of vertebrobasilar disease remain undiagnosed or are incorrectly diagnosed.[2] Some common symptoms, such as dizziness or transient loss of consciousness, are misattributed to posterior-circulation ischemia. Formerly, clinicians used the catchall term "vertebrobasilar insufficiency" to indicate a hemodynamic cause of all cases of posterior-circulation ischemia.[1,3,4] During the past 15 years, information provided by detailed clinical studies and brain imaging has revolutionized our understanding of the clinical aspects, causes, mechanisms, treatments, and prognosis of posterior-circulation ischemia.[1,3]

Causes and Vascular Lesions

The most common causes of vertebrobasilar ischemia are embolism, large-artery atherosclerosis, penetrating small-artery disease, and arterial dissection.[5-8] Migraine, fibromuscular dysplasia, coagulopathies, and drug abuse are much less frequent causes. Emboli arise from the heart, aorta, and proximal vertebral and basilar arteries.[1,3,5] The distribution of large-artery atherosclerosis differs according to race and sex.[9,10] White men often have atherosclerosis at the origin of the vertebral arteries from the subclavian arteries. Patients with atherosclerosis at this site often have carotid, coronary, and peripheral vascular disease.[9-13] Intracranial large-artery atherosclerosis is most common among blacks, Asians, and women.[1,9,10,12]

The small arteries that supply the brain stem and thalamus arise from the intracranial vertebral, basilar, and posterior cerebral arteries (Fig. 1). Hypertension increases the likelihood of lipohyalinotic thickening of these arteries, which, in turn, causes small infarcts.[14] Atherosclerosis of parent arteries can block or extend into the origins of these penetrating arteries or form microatheromas within these branches, leading to blockage (intracranial atheromatous branch disease).[15,16]

Dissections occur in the portions of the extracranial vertebral arteries that are most freely movable. These are the third portion of the vertebral artery that extends around the upper cervical vertebrae and the first portion of the vertebral artery between its origin and its entrance into the intervertebral foramina.[1,17,18]

Symptoms and Signs

Dizziness, vertigo, headache, vomiting, double vision, loss of vision, ataxia, numbness, and weakness involving structures on both sides of the body are frequent symptoms in patients with vertebrobasilar-artery occlusive disease. The most common signs are limb weakness, gait and limb ataxia, oculomotor palsies, and oropharyngeal dysfunction. Posterior-circulation ischemia rarely causes only one symptom but rather produces a

collection of symptoms and signs depending on which area is ischemic. Fewer than 1 percent of patients with vertebrobasilar ischemia in the New England Medical Center Posterior Circulation Registry (NEMC-PCR) had only a single presenting symptom or sign.[1,3,5]

COMMON PATTERNS OF PRESENTATION

EMBOLISM

The most frequent arterial sites of emboli are the intracranial vertebral arteries, which usually lead to cerebellar infarction, and the distal basilar artery, which leads to infarcts in the upper cerebellum, midbrain, thalamus, and territories of the posterior cerebral artery — so-called top-of-the-basilar infarcts.[1,3,5,19-22] Patients with cerebellar infarcts often report dizziness, occasionally in conjunction with frank vertigo, blurred vision, difficulty walking, and vomiting. They often veer to one side and cannot sit upright or maintain an erect posture without support. Patients may have hypotonia of the arm on the side of the infarct, a sign best elicited by having them hold their arms straight ahead and then rapidly lower them, quickly braking the movement. The hypotonic arm overshoots on both descent and rapid ascent. Nystagmus is common. Patients with pure cerebellar infarcts do not have hemiparesis or hemisensory loss.

Embolic infarcts can involve one posterior cerebral artery, which most often leads to a hemianopia of the contralateral visual field,[1,3,20,23] as in the patient described in Figure 2. The patient described in Figure 2 had occlusion of a vertebral artery causing transient ischemic attacks (TIAs) related to the lower brain stem and followed by an intraarterial embolus to the right posterior cerebral artery, causing an occipital-lobe infarct and a left hemianopia. Sometimes, hemisensory symptoms are present on the same side of the body and face as the hemianopia. Difficulty reading and naming colors often accompanies large infarcts of the left posterior cerebral artery, whereas neglect of the left visual field and disorientation to place may accompany infarcts of the right posterior cerebral artery. Bilateral infarcts of the posterior cerebral arteries cause bilateral visual-field defects and, sometimes, cortical blindness. Inability to make new memories as well as an agitated state can also occur.[1,3,21,22] Embolic infarction of the rostral midbrain and thalamus leads to a top-of-the-basilar syndrome characterized by somnolence and sometimes, stupor; inability to make new memories; small, poorly reactive pupils; and defective vertical gaze.[1,3,21,22]

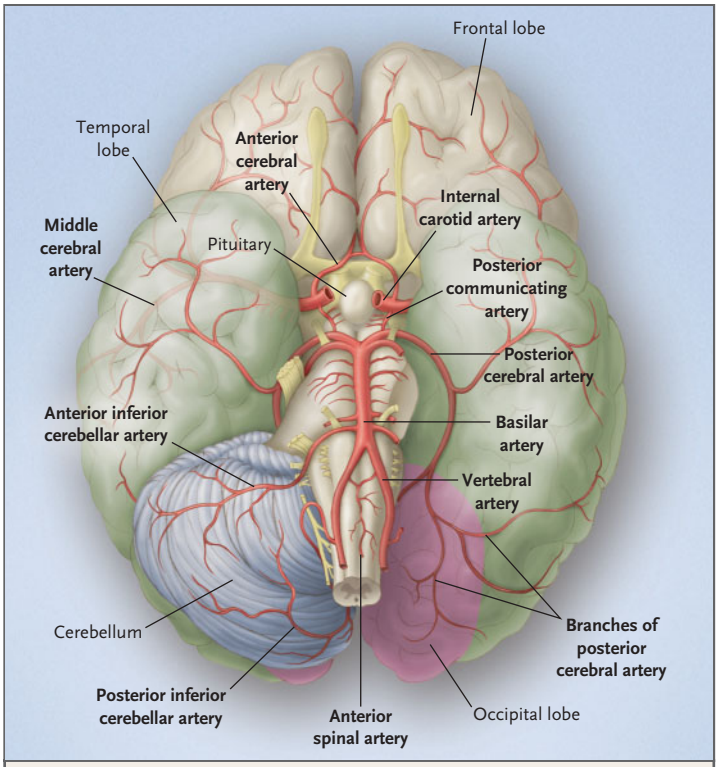

Figure 1. Arterial Supply of the Brain Stem, Cerebellum, Occipital Lobes, Posterior Temporal Lobes, and Thalamus.

The vertebrobasilar arterial supply feeds the brain stem (medulla, pons, and midbrain), cerebellum, occipital lobes, posterior temporal lobes, and thalamus (not visible in this view). The arterial supply consists of the extracranial and intracranial vertebral arteries, which unite to form the basilar artery, which runs midline along the ventral surface of the brain stem, feeding it with small, deep perforators until it merges with the circle of Willis to give off the posterior cerebral arteries.

ATHEROSCLEROTIC STENOSIS AND OCCLUSION

Atherostenosis at or near the origin of a vertebral artery in the neck is often manifested as brief TIAs, consisting of dizziness, difficulty focusing visually, and loss of balance.[13] Attacks occur after a patient has been standing or in situations that reduce blood pressure or blood flow. These symptoms are related to ischemia of vestibulocerebellar structures in the medulla and cerebellum.[13] In some patients, posterior cerebral, cerebellar, or top-of-the-basilar symptoms and signs occur suddenly, owing to embolism from the vertebral-artery occlusive lesion.

Atherostenosis or occlusion of an intracranial vertebral artery most often causes symptoms and

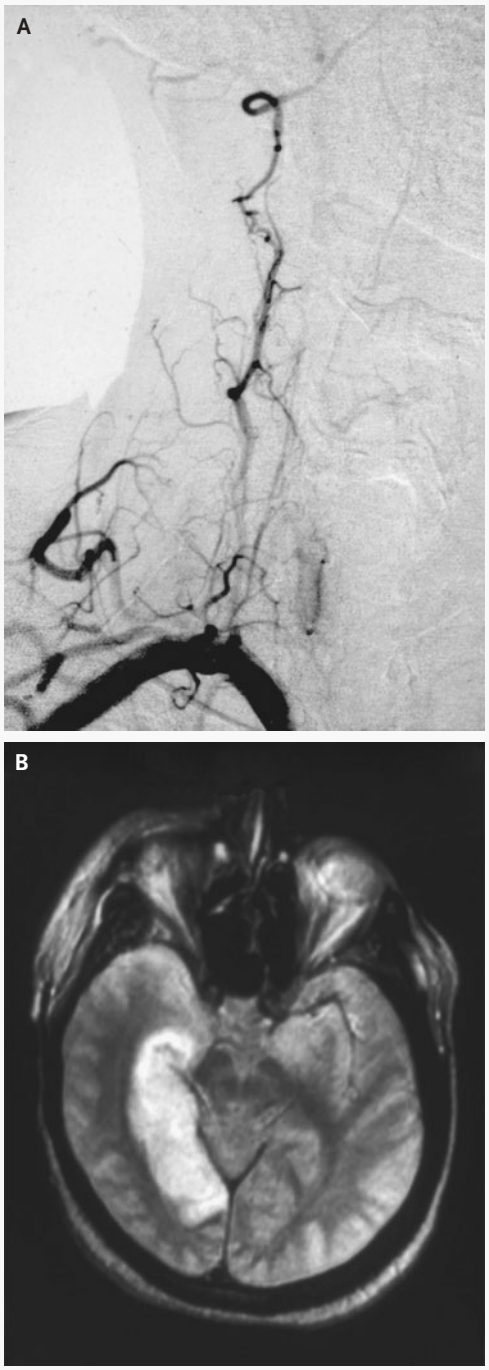

Figure 2. Patient with an Embolic Infarct.
A 57-year-old man with hypertension, high cholesterol levels, and angina pectoris awoke one morning and could not see to his left. During the preceding weeks, he had had several brief attacks of dizziness accompanied by difficulty focusing his eyes. During one spell, his body veered to the right. Examination showed a left homonymous hemianopia. A long, high-pitched bruit was heard in the right supraclavicular region. The angiogram showed extracranial vertebral-artery occlusion (Panel A). An embolus from the vertebral artery had migrated through the basilar artery to occlude the right posterior cerebral artery. Magnetic resonance imaging showed an occipital-lobe infarct (Panel B).

signs related to ischemia in the lateral medullary tegmentum, which are referred to as the Wallenberg, or lateral medullary, syndrome (Table 1 and Fig. 3A). Occlusion of an intracranial vertebral artery can also then become a source of emboli to the rostral basilar artery and its branches. When both intracranial vertebral arteries are compromised, the most frequent clinical pattern is spells of decreased vision and ataxia, often precipitated by standing or a reduction in blood pressure. In the NEMC-PCR, 13 of 407 patients had hemodynamically sensitive ischemia, most commonly caused by bilateral intracranial vertebral-artery occlusive disease, and they had multiple brief episodes of dizziness, veering, perioral paresthesias, and diplopia.[5,24]

Atherostenosis and occlusion of the basilar artery usually cause bilateral symptoms and signs or crossed findings (involving one side of the face and the contralateral side of the trunk and limbs).[1,3,25,26] Motor and oculomotor signs and symptoms predominate (Table 2) and, when severe, can cause the locked-in syndrome (Fig. 3B).

PENETRATING ARTERY DISEASE

Infarcts in the paramedian pons cause pure motor strokes characterized by weakness of the face, arm, and leg or arm and leg on one side without visual, sensory, cognitive, or behavioral abnormalities. At times, the weak limbs also show a cerebellar type of incoordination — an ataxic hemiparesis.[1,3,14-16] Thalamic lacunes present as pure sensory strokes with numbness or paresthesias involving the face, arm, and leg on one side without motor, visual, cognitive, or behavioral abnormalities.[1,3,14,16]

ARTERIAL DISSECTION

The cardinal symptom in patients with vertebral dissections is pain, most often in the posterior part of the neck or occiput, spreading into the shoulder.[1,17,18] Diffuse, mostly occipital, headache also occurs. Dizziness, diplopia, and signs of lateral medullary or cerebellar infarction can ensue from embolism or extension of the dissection to the intracranial vertebral artery. Intracranial vertebral-

artery dissections cause medullary, cerebellar, and pontine ischemia and can cause subarachnoid hemorrhage.[27]

SYMPTOMS NOT USUALLY CAUSED BY POSTERIOR-CIRCULATION DISEASE

Symptoms referable to systemic, circulatory, vestibular, and aural origins are often falsely attributed to posterior-circulation ischemia.

ISOLATED ATTACKS OF DIZZINESS, LIGHT-HEADEDNESS, OR VERTIGO

"Dizziness" may be used to refer to light-headedness, a lack of mental clarity, or frank vertigo. Vertigo indicates dysfunction of the peripheral vestibular or central vestibulocerebellar system. Vertigo in patients with peripheral vestibulopathies is often triggered by sudden movements and positional changes and is commonly associated with aural symptoms. Vertebral-artery disease can cause transient attacks of vertigo that are usually accompanied by other brain-stem or cerebellar symptoms. In our experience, isolated episodes of vertigo continuing for more than three weeks are almost never caused by vertebrobasilar disease. Rarely, and almost exclusively in patients with diabetes, occlusion of the branch of the anterior inferior cerebellar artery of the basilar artery supplying the inner ear can cause vertigo, unilateral hearing loss, or both before causing brain-stem infarction.[28]

Light-headedness usually reflects presyncope related to circulatory, systemic, or cardiac disease. In the absence of neurologic symptoms or signs, light-headedness is rarely a manifestation of vertebrobasilar ischemia. The diagnostic yield of neurovascular testing (neuroimaging and ultrasonography) in patients with isolated syncope is very low.[29] Isolated syncope poses no increased risk of stroke.[30] Only 7 percent of the 407 patients in our series described light-headedness, and none presented with light-headedness as an isolated symptom.[1,3,5]

TRANSIENT DECREASE IN CONSCIOUSNESS

Seizures and syncope are much more common causes of temporary loss of consciousness than is cerebrovascular disease. The reticular activating system, which promotes wakefulness, is located in the paramedian tegmentum of the upper brain stem. Basilar-artery occlusions can interrupt the function of these fibers and impair consciousness. Coma may occur. However, basilar occlusive disease always causes other accompanying findings, such as oculomotor and motor signs.

Table 1. Signs and Symptoms of Lateral Medullary Infarct.

General Symptoms	Ipsilateral Signs	Contralateral Signs
Dizziness, vertigo		
Facial pain	Decreased pain and temperature sensations in face	Decreased pain and temperature sensations in trunk, limbs, or both
	Horner's syndrome	
Difficulty sitting without support, veering to one side	Limb ataxia	
Hoarseness	Laryngeal paralysis	
Dysphagia	Pharyngeal paralysis	

DROP ATTACKS

A drop attack is defined as a sudden loss of postural tone and falling without warning. Associated loss of consciousness implicates syncope or seizures as the cause. Drop attacks have inappropriately been attributed to transient ischemia of the posterior circulation. Brain-stem ischemia can affect corticospinal tracts subserving motor control of the limbs, but when it does so, it usually causes persistent weakness. Not a single patient in the NEMC-PCR had a drop attack as the only symptom.[1,3,5] In the absence of symptoms or findings that suggest brain-stem or cerebellar dysfunction, posterior-circulation ischemia is rarely the cause of drop attacks.

EVALUATION OF PATIENTS WITH SUSPECTED POSTERIOR-CIRCULATION ISCHEMIA

Thorough evaluation of a patient's history and findings on physical and neurologic examinations should provide guidance regarding which investigations to perform. All patients in whom vertebrobasilar-territory strokes or TIAs are suspected should undergo neuroimaging, preferably magnetic resonance imaging (MRI), because computed tomography (CT) provides less complete visualization of the brain stem, owing to artifacts related to the skull. MRI with diffusion-weighted imaging is the most sensitive test available to detect acute infarcts. Most patients with posterior-circulation strokes and some patients with TIAs related to the posterior-

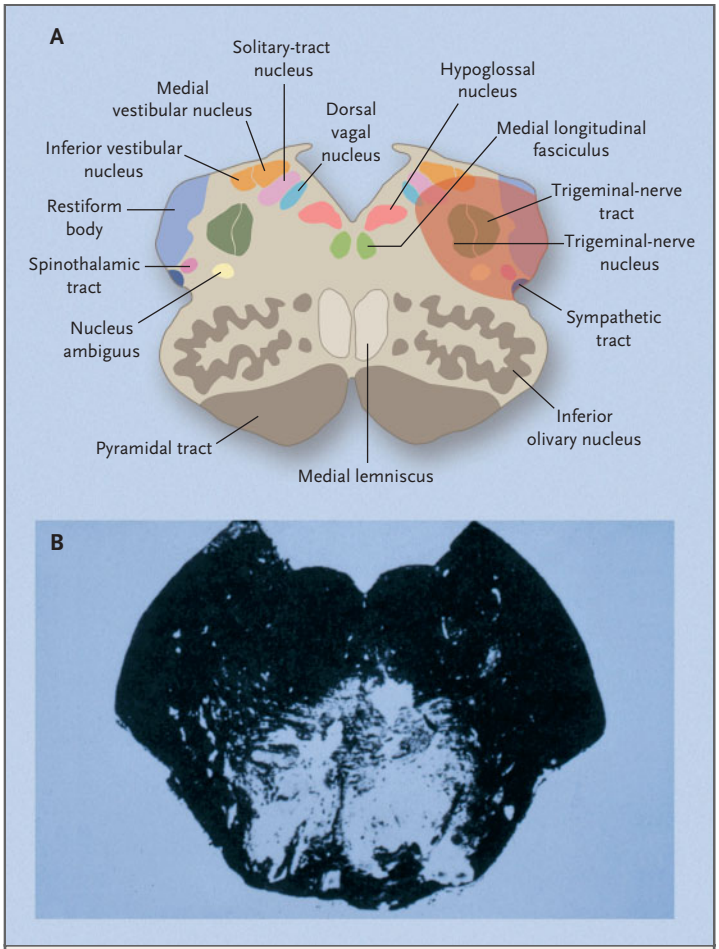

Figure 3. Two Types of Vertebrobasilar Infarcts.

Panel A shows the portions of the brain affected by the Wallenberg syndrome, which is an infarction of the lateral portion of the medullary tegmentum. The most common cause is occlusion of the intracranial vertebral artery. Symptoms and signs are described in Table 1. Panel B shows the histopathological findings at autopsy in a patient who had extensive bilateral infarction of the pons as a result of a basilar-artery embolism (Luxol fast blue). The extracranial vertebral artery was dissected in a skiing accident, and a thrombus subsequently developed, which migrated to the basilar artery, causing severe limb and facial paralysis and leaving the patient able only to move her eyes up and down in order to communicate (referred to as the locked-in syndrome).

circulation territory that last more than an hour show acute lesions on diffusion-weighted imaging.[31-33] Rarely, diffusion-weighted imaging may be normal in patients with an acute vertebrobasilar stroke, but such a result does not exclude infarction. Follow-up studies often reveal infarcts matching the clinical presentation.[34] Magnetic resonance angiography can be used to identify the location and severity of occlusions in the large arteries of the neck and intracranial lesions.[31,35]

Patients with pacemakers or other circumstances that do not permit the use of MRI should undergo CT and CT angiography unless such approaches are contraindicated. High-quality CT angiography can be used to delineate the extracranial and intracranial posterior circulation and is very helpful for evaluating patients with suspected basilar-artery occlusion.[36] Duplex ultrasonography can also be used to show the proximal vertebral arteries,[37] and Doppler studies of the vertebral arteries in the neck can reveal whether blood flow is antegrade or reversed. Transcranial Doppler studies can be used to show occlusive lesions in the intracranial vertebral and proximal basilar arteries. Ultrasonography of the carotid arteries is seldom useful in the evaluation of patients with posterior-circulation ischemia. In rare cases of embolism, the posterior cerebral artery arises anomalously directly from the intracranial carotid artery.

Cardiac investigations including electrocardiography, echocardiography, and rhythm monitoring are important parts of the evaluation to search for cardiac and aortic sources of the embolism, especially in patients with no cervicocranial occlusive lesions that explain the symptoms and signs and in patients with multiple brain infarcts in different vascular territories.

Screening blood and coagulation tests should include a complete blood count and coagulation studies. Other tests for genetic and acquired coagulopathies and measurement of antiphospholipid antibodies may be appropriate in patients who have a history suggesting prior venous or arterial occlusions or in those in whom no cardiac, aortic, or cervicocranial lesions are found.

Accurate diagnosis of the specific type of stroke and vascular and brain lesions requires the following: a demographic assessment (age, race, and sex) and an evaluation of risk factors for stroke; knowledge of the course of symptoms (for example, whether the stroke was preceded by a single or multiple varied or stereotypical TIAs, whether the onset was sudden and not preceded by TIAs, and whether the ischemia is progressive); matching of the patient's symptoms and signs to known pattern of ischemia; and brain and vascular imaging.

PROGNOSIS

The outcome of vertebrobasilar stroke depends on the severity of the neurologic signs, the presence or absence of arterial lesions, the location and extent

Table 2. Signs and Symptoms of Basilar-Artery Occlusion.

Corticospinal
Limb weakness (often bilateral)
Limb hyperreflexia
Extensor plantar response
Corticobulbar
Facial weakness
Dysarthria
Dysphagia
Increased gag reflex
Oculomotor
Diplopia
Gaze palsies
Nystagmus
Internuclear ophthalmoplegia
Reticular activating system
Reduced consciousness

of infarction, and the mechanism of ischemia.[1,38] The rate of death immediately after posterior-circulation stroke is approximately 3 to 4 percent.[38,39] In the NEMC-PCR, 3.6 percent of patients died, and 18 percent of patients had a major disability.[38] Cardiac embolism, basilar-artery involvement, and the involvement of multiple intracranial territories increase the risk of a poor outcome irrespective of the patient's age and underlying risk factors.[38] Basilar-artery occlusive disease carries a high risk of disability and death, and efforts should be directed at identifying this lesion as quickly as possible.[1,26,38]

IMMEDIATE AND PREVENTIVE THERAPY

Various medical, interventional, and surgical approaches are available to treat ischemia of the posterior circulation of the brain, but none have been thoroughly tested in randomized trials. The potential treatments are the same as those used for ischemia of the anterior circulation of the brain. However, few trials have classified patients with ischemic stroke according to whether they have anterior-circulation or posterior-circulation disease. Among the trials that have done so, only a handful have evaluated and reported the cardiac, arterial, and hematologic causes of the strokes.

SHORT-TERM MEDICAL MANAGEMENT

The National Institute of Neurological Disorders and Stroke (NINDS) trial showed that intravenous administration of tissue plasminogen activator (t-PA) enhances neurologic recovery from ischemic stroke when administered within three hours after the onset of stroke, after brain hemorrhage has been excluded on the basis of CT.[40] Three studies of the intravenous administration of thrombolytic agents for vertebrobasilar disease reported mixed results.[41-43] Following the NINDS guidelines, Grond et al. treated 12 patients with t-PA within three hours after the onset of stroke. Ten of the 12 patients had favorable outcomes, 1 had a poor outcome, and 1 died.[41] In another study of five patients who received t-PA within six hours after the onset of symptoms,[42] two patients had minor partial reperfusion and one had complete reperfusion. Three of the patients died, and one remained "locked-in." Montavont et al. treated 18 patients within seven hours after the onset of stroke.[43] Three months after treatment, 10 of the 18 patients were independent (i.e., they were able to look after themselves with no or only slight disability), but 2 had died and the condition of 6 was poor.[43]

Thrombolytic agents are also administered intra-arterially through a catheter directed to the thrombus. In a retrospective study of 65 patients with vertebrobasilar occlusions, the 43 patients given urokinase or streptokinase — two thirds of whom were treated within 24 hours after the onset of stroke — had better survival rates and more favorable outcomes than the 22 patients who were treated with antithrombotic agents. Among the patients who were given thrombolytic agents, only those in whom the occlusive artery recanalized survived.[44] In nine additional reports, among 285 patients who were mostly given t-PA more than eight hours after the onset of stroke,[45] 62 percent had good recanalization and 28 percent of the overall population subsequently did well. Brandt et al. found that among 51 patients who underwent thrombolysis for acute vertebrobasilar lesions, those with embolic occlusions that were short and involved the proximal basilar artery with good collateral arteries were most likely to have recanalization and a good outcome. Patients who were comatose or tetraplegic or who had chronic white-matter abnormalities had poor outcomes.[46]

Clinicians have insufficient data to guide the choice between intravenous and intraarterial thrombolytic therapy for vertebrobasilar ischemia. If patients present within three hours after the onset of symptoms, some neurologists follow NINDS guidelines and administer t-PA intravenously after CT has excluded hemorrhage. We favor brain and vascular imaging (CT with CT angiography or diffusion-

weighted MRI with magnetic resonance angiography) before deciding whether to use thrombolysis, especially if more than three hours has passed since the onset of symptoms or the diagnosis is uncertain. If a vertebral-artery occlusion is found, we give intravenous t-PA. When imaging studies suggest basilar-artery occlusion, we recommend cerebral angiography and intraarterial thrombolysis, because basilar-artery occlusions carry an increased risk of death and disability and there is extensive experience with intraarterial thrombolysis, even if it is given 12 to 24 hours after the onset of stroke in this condition.[44,45]

Some patients with intracranial vertebrobasilar occlusive disease are very sensitive to changes in brain perfusion from decreases in blood pressure or blood volume, and even from sitting up or standing.[24,47] In these patients, maximizing blood flow and blood volume by using fluids and pressors is important.

PREVENTION

Strong evidence from randomized, controlled trials provides support for the efficacy of anticoagulation with warfarin to prevent subsequent cerebrovascular events in patients with embolic stroke of cardiac origin. In a retrospective comparison of the effectiveness of warfarin and aspirin among 68 patients with symptomatic intracranial-artery stenosis that was arteriographically documented, warfarin was superior in patients with vertebrobasilar occlusive disease.[48] However, a prospective, double-blind study involving patients with symptomatic intracranial stenosis of 50 to 99 percent, which was prematurely terminated after the randomization of 569 patients to warfarin or aspirin (1300 mg), showed that both agents were equally effective but that warfarin caused significantly more serious hemorrhages.[49] The Warfarin–Aspirin Recurrent Stroke Study of secondary prevention also showed that aspirin and warfarin were equally efficacious in patients with noncardioembolic stroke.[50]

The results of prospective trials showed that antiplatelet agents (aspirin, ticlopidine, clopidogrel, dipyridamole, and the combination of aspirin and dipyridamole) were beneficial in series of patients with TIAs and strokes. However, only two studies analyzed the findings in relationship to arterial territories, and none reported the nature of the vascular occlusive lesions. Ticlopidine was superior to aspirin for secondary cerebrovascular protection, especially in patients with symptomatic posterior-circulation disease.[51] In the European Stroke Prevention Study, among patients with clinically documented vertebrobasilar-territory TIAs or strokes, strokes occurred in 5.7 percent of 255 patients treated with the combination of aspirin and modified-release dipyridamole, as compared with 10.8 percent of patients who received placebo (P=0.005).[52]

We treat patients with large-artery stenosis and small-artery disease with antiplatelet agents. For patients with severe, large-artery, flow-limiting stenosis and vertebral-artery dissection,[18] we consider treatment with anticoagulants in order to prevent distal embolization and progression of infarcts. When imaging shows atherosclerotic plaques, we also prescribe statins unless the patient has a low-density lipoprotein cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter).[53] Patients with large-artery atherostenosis who continue to have ischemic events while receiving medical therapy are referred for surgery, angioplasty, or stenting, depending on the nature and location of the arterial lesions (see below). Randomized trials should be designed to address which therapeutic options are most appropriate for specific stroke mechanisms and arterial occlusive lesions.

FUTURE DIRECTIONS

ENDOVASCULAR PROCEDURES

Evidence provided by scattered case series suggests that vertebrobasilar angioplasty and stenting may become important therapeutic strategies for large-artery vertebrobasilar disease. Preliminary results of angioplasty or stenting of occlusive vertebral-artery lesions in the neck show that restenosis is more common than with carotid-artery stenting.[54] The small diameter and angulation of the vertebral-artery origin complicate endovascular treatment. Intracranial vertebral- and basilar-artery angioplasty and stenting have produced mixed results, with a relatively high rate of complications.[55] Although the results are preliminary, mechanical removal of thromboemboli may become potentially useful in patients who cannot receive thrombolytic drugs and as an adjunct to thrombolysis.[56] We await large, controlled trials comparing endovascular revascularization with various medical therapies.

SURGERY

Endarterectomy for severe extracranial vertebral-artery disease has low rates of complications and mortality when performed by surgeons with ex-

tensive experience.[57] The indications for vertebral-artery surgery are still uncertain. Before the advent of intracranial angioplasty, bypass shunts were surgically created between extracranial arteries and the intracranial posterior circulation, with some success, but no trials were undertaken to prove their effectiveness.[1]

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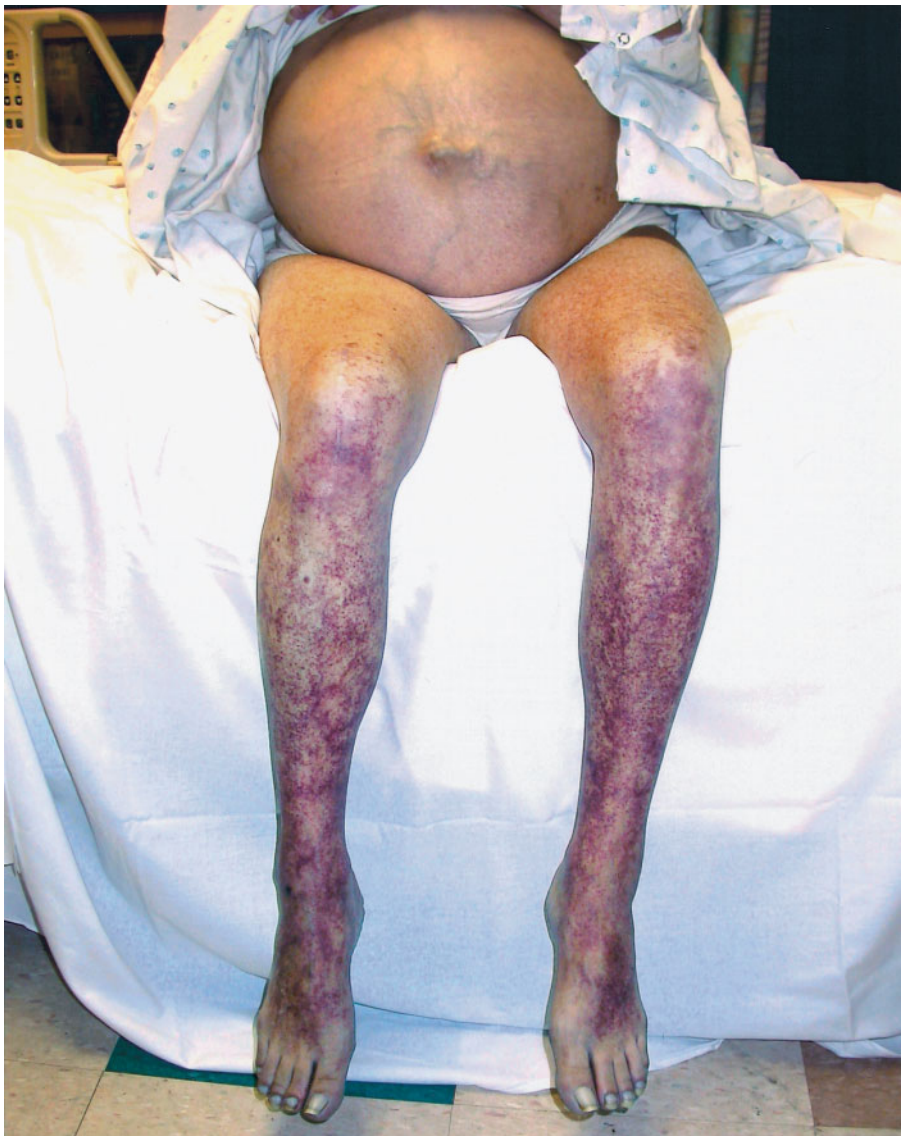
IMAGES IN CLINICAL MEDICINE

Mixed Cryoglobulinemia



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A 38-year-old woman presented with increasing abdominal fullness and a new rash on the lower extremities. She had a history of chronic hepatitis C infection, for which she had been treated with interferon alfa several years earlier. She had a remote history of alcohol and intravenous drug use. On physical examination, ascites, caput medusae, spider hemangiomas, and palpable lesions on the legs and feet were noted. Laboratory evaluation revealed an albumin level of 1.0 gm per deciliter, an international normalized ratio of 2.3, the presence of cryoglobulins, a positive result on testing for hepatitis C antibody, and a negative result for antibodies to hepatitis B virus and the human immunodeficiency virus. The patient was admitted, and during hospitalization, acute renal failure and pancytopenia developed. She underwent plasmapheresis, with improvement of her rash and of renal and bone marrow function.

Hepatitis C is the most important cause of mixed cryoglobulinemia. This extrahepatic manifestation of hepatitis C infection is typically responsive to antiviral therapy.

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 19-2005: A 17-Year-Old Girl with Respiratory Distress and Hemiparesis after Surviving a Tsunami

Ann Y. Kao, M.D., Rus Munandar, M.D., Stephen L. Ferrara, M.D., Lt. Comdr., David M. Systrom, M.D., Robert L. Sheridan, M.D., Sydney S. Cash, M.D., Ph.D., and Edward T. Ryan, M.D.

From the Department of Medicine, Chelsea Health Center (A.Y.K.), the Pulmonary and Critical Care Unit (D.M.S.), the Department of Neurology (S.S.C.), and the Tropical & Geographic Medicine Center, Division of Infectious Diseases (E.T.R.), Massachusetts General Hospital, Boston; Project HOPE, Task Force HOPE–*Mercy* (A.Y.K., D.M.S., R.L.S., S.S.C., E.T.R.); the Departments of Medicine (A.Y.K., D.M.S., E.T.R.), Surgery (R.L.S.), and Neurology (S.S.C.), Harvard Medical School, Boston; the Department of Medicine, Zainoel Abidin University Hospital, Banda Aceh, Sumatra, Indonesia (R.M.); the Department of Radiology, U.S. Naval Ship *Mercy* T-AH19, and the Department of Radiology, Naval Medical Center, San Diego, Calif. (S.L.F.); and the Burn and Trauma Services, Massachusetts General Hospital and the Shriners Hospital for Children, Boston (R.L.S.).

N Engl J Med 2005;352:2628-36.

Editor's note: After the earthquake and tsunami in the Indian Ocean on December 26, 2004, the Massachusetts General Hospital formed a clinical-response team to work with Project HOPE (Health Opportunities for People Everywhere). Project HOPE volunteers worked with U.S. Navy and Public Health Service personnel on the hospital ship, U.S. Naval Ship (U.S.N.S.) *Mercy* T-AH19 in Operation Unified Assistance, off the coast of Banda Aceh, Sumatra, Indonesia. This conference took place on April 14, 2005, with teleconferencing to the U.S.N.S. *Mercy*, stationed near Nias Island, Indonesia, the site of another earthquake on March 28, 2005.

PRESENTATION OF CASE

Dr. Ann Y. Kao: A 17-year-old, right-handed girl was transferred from Zainoel Abidin University Hospital, Banda Aceh, Sumatra, Indonesia, to the U.S.N.S. *Mercy* off the coast of Banda Aceh, because of respiratory distress and hemiparesis.

The patient had been well until seven weeks earlier, when she had been swept up by the tsunami that struck the Indonesian coast. She was engulfed by the wave outside her house, 2.5 km inland, and was carried approximately 1 km. She did not lose consciousness but she aspirated water and mud. She was found by friends at a camp for internally displaced persons, and they took her to a relative's house. Two days after the tsunami, she was examined at a local clinic for a cough, treated, and released. The next week, she was reunited with her father. Headache, nausea, and vomiting developed, and her appetite decreased. Approximately two weeks after the tsunami, her father took her to a local clinic, where pneumonia was diagnosed. Unknown medications were administered.

One week later, approximately four weeks before admission, weakness in the right side of the face, right arm, and leg developed; the girl stopped speaking, had difficulty swallowing, and choked while eating. She was admitted to the International Committee of the Red Cross–Crescent field hospital. On examination, she was hypotensive, with flaccid paralysis of the right side. A chest radiograph revealed air-space consolidation with a small pleural effusion on the right side. Combination therapy with meropenem

and trimethoprim–sulfamethoxazole was begun. The weakness progressively increased.

The day before admission, the patient was transferred from the field hospital to Zainoel Abidin University Hospital and cared for by Indonesian and Australian providers. A physical examination revealed that the right arm and leg were flaccid; reflexes were more brisk on the right side than on the left side. Chest radiography revealed consolidation with a small right-sided pleural effusion. An analysis of cerebrospinal fluid showed 400 erythrocytes per cubic millimeter and no leukocytes. Staining for the presence of bacteria, mycobacteria, and fungi was negative. The patient was transferred to the hospital ship U.S.N.S. *Mercy* for further evaluation.

The patient had had normal growth and development. She had no allergies, and her vaccination status was unknown. Her father and two adult siblings were alive and well; her mother and a cousin had died in the tsunami.

On examination, the patient was alert and cooperative with a flat affect, and she appeared younger than her age (Tanner developmental stage 2 to 3, with 1 representing immature development and 5 maturity). The blood pressure was 109/66 mm Hg, the pulse 112 beats per minute, the temperature 37.0°C, and the respiratory rate 20 breaths per minute with slight nasal flaring. The oxygen saturation was 93 percent while she was breathing ambient air. The mucous membranes were dry. The breath sounds were diminished over the lower right lung field and in the left base, and crackles and rhonchi were present in the left base. Her extremities were cool to the touch, with prolonged capillary refill of 4 to 5 seconds. She was able to follow simple commands but spoke little, did not repeat words when asked, and had difficulty naming objects. The pupils were round and reactive to light, the extraocular movements were intact, and the fundi were normal. There was a right-sided facial droop and flaccid paralysis of the right arm and right leg. Her sensation of light touch was intact, and the reflexes were 3+ on the right and 2+ on the left. There was a Babinski reflex of the right big toe; her gait and stance were not tested. The remainder of the examination was normal.

The serum levels of electrolytes and the results of renal- and liver-function tests were normal; the results of hematologic laboratory tests are shown in Table 1. A chest radiograph obtained with portable equipment when the patient was in a semirecumbent position showed a large, left-sided pneumothorax with a left apical cavity that measured 2.7 cm by 2.4 cm and did not have an air–liquid level. There were air-space infiltrates in the lingula and right upper lobes. A chest tube was placed that drained pleural fluid that was turbid and yellow; laboratory tests showed levels of glucose of 93 mg per deciliter (5.2 mmol per liter), total protein 4.0 g per deciliter, lactate dehydrogenase 901 U per liter, white-cell count 211 per cubic millimeter (79 percent polymorphonuclear cells, 12 percent mononuclear cells, and 9 percent eosinophils), and red-cell count 1210 red cells per cubic millimeter. Gram's staining, acid-fast staining, and staining for fungi revealed no organisms. A repeated chest radiograph showed a decrease in the size of the pneumothorax, with nearly full expansion of the left lung.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Laurence Ronan (Medicine): This child was cared for by Indonesian and Australian providers at Zainoel Abidin University Hospital in Banda Aceh under the direction of Dr. Rus Munandar, the director and physician-in-chief, and then by physicians from this hospital aboard the U.S.N.S. *Mercy*. Dr. Munandar is unable to be with us today but has asked that the following statement be read on his behalf.

Table 1. Hematologic Laboratory Findings.

Variable	Day of Admission to U.S.N.S. *Mercy*	Third Hospital Day
Hematocrit (%)	50.3	25.4
Hemoglobin (g/dl)	17.3	8.8
White-cell count (per mm³)	6,300	8,200
Differential count (%)		
Neutrophils	45	61
Lymphocytes	45	27
Monocytes	4	4
Eosinophils	5	7
Basophils	1	
Platelet count (per mm³)	163,000	382,000
Mean corpuscular volume (μm³)	83.0	

Despite the fact that many of the staff at our hospital lost family, friends, and colleagues in the earthquake and tsunami, we began rebuilding the hospital and accepting patients within one day of the tsunami. Over the past few months, we have cared for patients with wound infections and aspiration pneumonias directly related to the tsunami, as well as for patients with many other medical conditions directly or indirectly related to the tragedy. We appreciate the help and support we have received from our Indonesian colleagues, as well as from the international community.

Because our hospital had no working computed tomographic (CT) scanner, this patient was transferred for further evaluation to the U.S.N.S. *Mercy*.

Dr. Kao: When I first saw this patient in our casualty receiving area, she was withdrawn and would not make eye contact. She had decreased oxygen saturation and severe dehydration. Her speech was not intelligible to our interpreters. She had a right-sided facial droop, flaccid paralysis of the right arm and leg, with brisk reflexes and preserved sensation (Fig. 1A). My primary concern was her respiratory status. It was not clear how long the pneumothorax had been present, and although she was hemodynamically stable, she appeared to be tiring. My other concern was whether whatever intracranial process was causing hemiparesis could lead to increased intracranial pressure and herniation of the brain. A less immediate concern was how withdrawn and profoundly sad she appeared, and I wondered if she was already suffering from post-traumatic stress disorder.

The diagnostic procedures were imaging studies of the chest and head.

Lt. Comdr. Stephen L. Ferrara, M.D.: The chest radiograph obtained at the patient's admission shows a large, left-sided pneumothorax, a round left apical cavity, 2.4 cm by 2.7 cm, and bilateral pulmonary infiltrates (Fig. 2A). I placed a chest tube on the left side, and after reexpansion of the lung, the cavity and infiltrates can be seen more clearly (Fig. 2B). CT scanning of the head after the administration of contrast material revealed four well-demarcated ring-enhancing lesions in the left cerebral hemisphere, some in the gray matter and some in the white matter, with extensive surrounding vasogen-

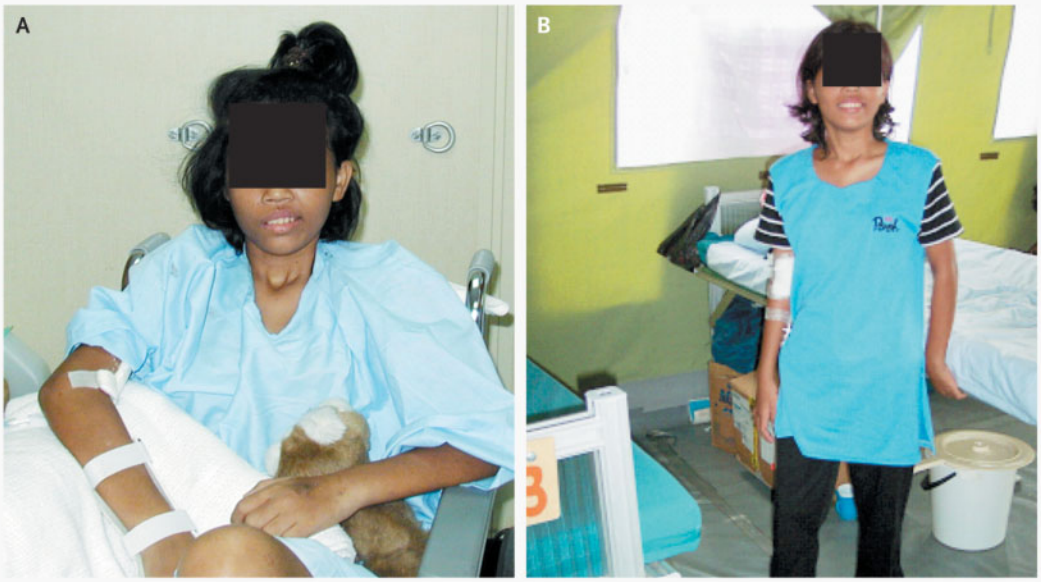

Figure 1. Photographs of the Patient.
On admission, the patient was withdrawn and appeared sad, with a right-sided facial droop and flaccid paralysis of the right arm and leg (Panel A). After her discharge from the U.S.N.S. *Mercy* to the International Committee of the Red Cross–Crescent field hospital, the facial droop was gone, and she was able to stand unassisted (Panel B). (The photograph in Panel B is courtesy of Comdr. Karen Niemantsverdriet McDonald, assistant director of nursing services, U.S.N.S. *Mercy*.)

ic edema (Fig. 2C and 2D). Despite the multiplicity of the lesions, they are all located in the left cerebral hemisphere and spare the corticomedullary junction. This constellation of findings is consistent with infection by an aggressive, cavity-forming organism, which gained access to the bloodstream and has spread hematogenously to the central nervous system and resulted in the formation of brain abscesses.

Dr. Kao: We were fortunate to have many consultants aboard the ship, and nearly simultaneously we had a pulmonologist, a surgeon, a neurologist,

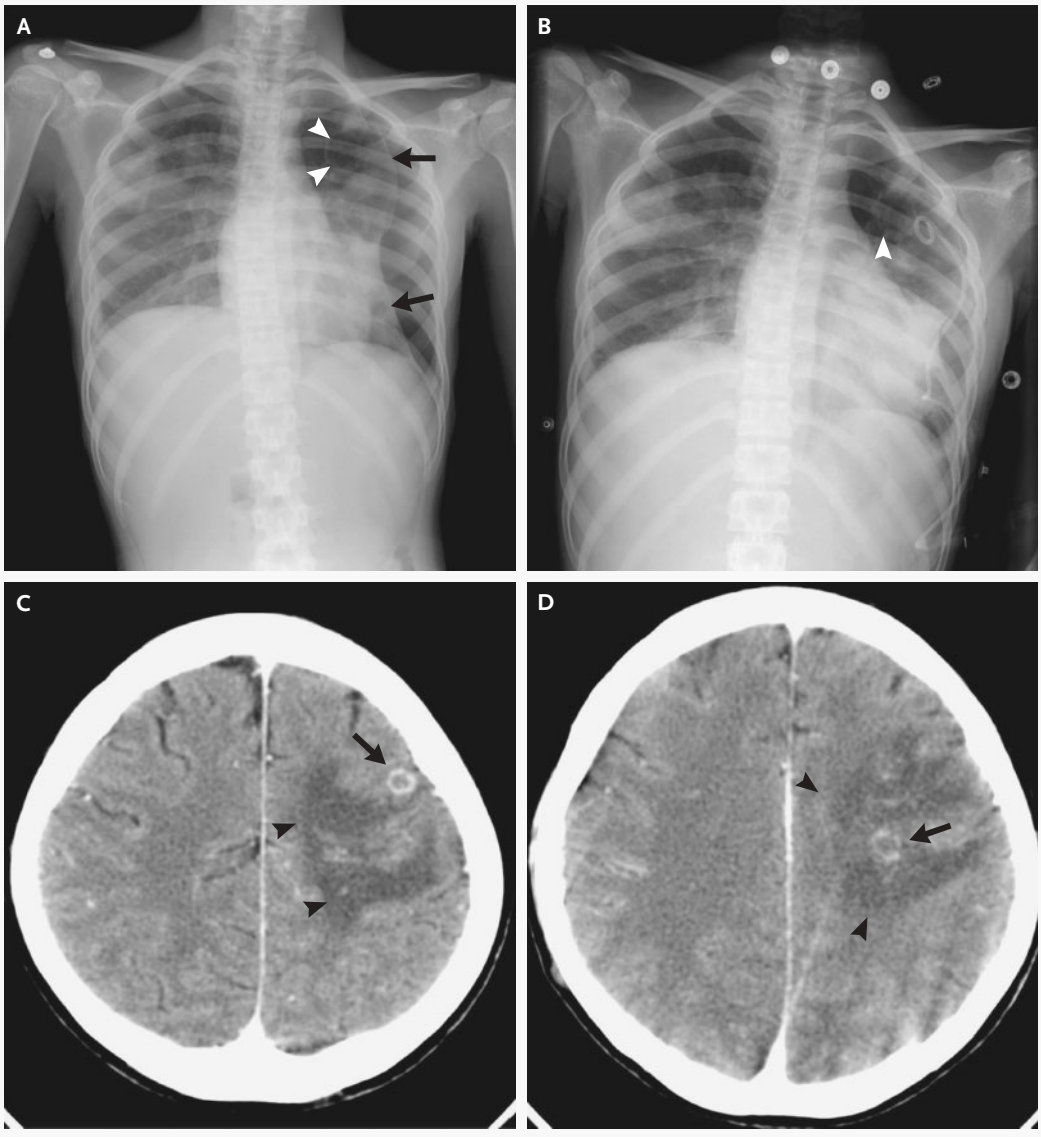

Figure 2. Radiographic Studies.

On the chest radiograph obtained while the patient was in the semirecumbent position with portable equipment on admission (Panel A), there is a large, left-sided pneumothorax (arrows), a left apical cavity (arrowheads), and bilateral air-space infiltrates in the lingula and in the right upper lobe abutting a minor fissure. Another chest radiograph obtained immediately after left-tube thoracostomy (Panel B) shows partial reexpansion of left lung; the cavitary lesion (arrowhead) and bilateral air-space infiltrates are seen more easily. Images from contrast-enhanced CT of the patient's head show ring-enhancing lesions in gray matter (Panel C, arrow) and white matter (Panel D, arrow) of the left cerebral hemisphere with surrounding edema (arrowheads, Panels C and D).

and a specialist in infectious diseases and tropical medicine at the patient's bedside.

DIFFERENTIAL DIAGNOSIS OF THE PULMONARY PROCESSES

Dr. David M. Systrom: As the pulmonary consultant, I needed to consider four aspects of this case: the near-drowning episode in the tsunami, cavitary pulmonary parenchymal disease, the left-sided pneumothorax, and the findings in the pleural fluid. Ordinarily, the discussant at these exercises casts a wide differential diagnostic net that is progressively cinched. In this case, the history of aspiration from a 65-foot black wave allows for a more focused discussion.

Submersion Injury

In a submersion injury,[1] the victim initially voluntarily closes the glottis. Involuntary laryngospasm ensues, during which time the victim may swallow large amounts of seawater that may be aspirated subsequently during bouts of vomiting. This reflex for airway protection results in a surprisingly small amount of liquid being aspirated, generally on the order of 3 to 4 ml per kilogram of body weight. Thus, electrolyte abnormalities, which used to be considered a major problem after a near-drowning, are uncommon, because aspiration of at least twice that volume would be required to alter the levels of electrolytes. Aspirated fluid can disrupt surfactant and initiate an inflammatory response that results in chemical pneumonitis, acute lung injury, and in severe cases, the acute respiratory distress syndrome. This patient's cough, which was noted at the clinic two days after the tsunami, is consistent with chemical irritation of the airway. Chronic sequelae of near-drowning include a hyperreactive airway syndrome and chronic pulmonary infection; the occurrence of the latter is dependent on the inoculum of contaminated liquid and on host defenses, which may have been impaired in this patient because of malnutrition. The respiratory problems that our patient had two weeks after the tsunami and that persisted to her admission are probably the result of chronic pulmonary infection.

Cavitary Lung Disease

True cavities of the lung occur as a result of developmental abnormalities of the foregut and when neoplastic or inflammatory processes destroy lung tissue. Some diseases associated with large single cavities of the pulmonary parenchyma are listed in Table 2. In this patient, aspiration of contaminated seawater weeks earlier strongly suggests that chronic necrotizing bacterial pneumonia was responsible for the cavitary lung disease. Preexisting disease, either a condition discovered incidentally or one that worsened as a result of malnutrition or loss of medical infrastructure, is also possible. *Mycobacterium tuberculosis* was a concern in this case and could have accounted for all of the clinical and radiographic features; however, acid-fast staining of sputum, pleural fluid, and cerebrospinal fluid was negative.

Pneumothorax

This patient had both a large, left-sided pneumothorax and liquid in the pleural space, a hydropneumothorax. Blunt trauma to the chest or abdomen — common during the tsunami because of floating debris and deceleration against fixed structures — could have forced air into the pulmonary interstitium and pleural space after an abrupt rise in alveolar pressure against a closed glottis. Because an earlier chest radiograph did not show a pneumothorax, however, it is more likely that in this case rupture of the left upper-lobe cavity through visceral pleura caused a secondary pneumothorax. In this patient, after the chest tube was placed, an air leak persisted for two to three days after admission, which indicated that there was a bronchopleural fistula and supported the diagnosis of secondary pneumothorax.

Parapneumonic Pleural Effusion

The finding of elevated levels of lactate dehydrogenase in the pleural fluid met the criteria for an exudate, which the patient's history and chest radiograph suggest was parapneumonic in nature. The American College of Chest Physicians guidelines[2]

Table 2. Causes of Cavitary Lung Lesions.

Category	Disease
Developmental	Sequestration
Malignant	Bronchogenic carcinoma Lymphoma
Noninfectious, inflammatory	ANCA-associated vasculitis* Sarcoidosis Rheumatoid nodules Silicosis
Infectious	Mycobacteria Parasites Fungi Bacteria

* ANCA denotes antineutrophil cytoplasmic autoantibodies.

for the treatment of parapneumonic effusions emphasize the need for an aggressive approach when there is pleural thickening or loculations, positive microbiologic evaluations (gross pus or positive Gram's stain or culture), a pH less than 7.20, or a glucose level less than 60 mg per deciliter. In this patient, the hydropneumothorax mandated closed thoracoscopy and chest-tube drainage, which were done.

In summary, the history of aspiration in the tsunami followed by cavitary lung disease, secondary pneumothorax, and complicated parapneumonic effusions is best explained by chronic necrotizing aspiration pneumonia, also referred to as tsunami-related aspiration pneumonia.

SURGICAL MANAGEMENT OF ADVANCED LOCAL CONSEQUENCES OF BACTERIAL PNEUMONIA

Dr. Robert L. Sheridan: The surgical objectives to address empyema can be divided into two basic categories: evacuation of the infected pleural contents and elimination of the resulting closed space.[3] As the infectious process becomes increasingly chronic, the procedures required to attain these objectives become increasingly difficult.

If the infected pleural fluid is thin and the underlying lung parenchyma pliable, both objectives can be achieved by closed catheter drainage, as in the case under discussion. If the infected material is thick, open drainage and manual removal of fibrinous exudate may be required. This is now often accomplished with the minimally invasive technique of video-assisted thoracoscopy.[4] In cases of chronic empyema, decortication may be necessary to allow the entrapped lung to come up to the chest wall. If the underlying lung is destroyed by infection, it may be necessary to convert the closed pleural space to an open sinus (Eloesser flap), to bring the chest wall down to the remnant lung (thoracoplasty), or to fill the void with vascularized muscle flaps.[5,6] Fortunately, these procedures are rarely required in the developed world.

NEUROLOGIC DIFFERENTIAL DIAGNOSIS

Dr. Sydney S. Cash: This young woman's neurologic findings were primarily progressive motor (Broca's) aphasia and right hemiparesis, with upper motor-neuron signs but no sensory deficits, in a setting of prior trauma and aspiration pneumonia. These findings pointed to a lesion involving the left frontal cortex, the subjacent white matter, or both, and descending corticospinal tracts.

Whereas the clinical context, temporal profile, and imaging findings allowed us to narrow down the diagnosis to probable bacterial brain abscess, the differential diagnosis for this clinical picture includes a variety of space-occupying, infiltrating, or inflammatory processes (Table 3). Fungal and parasitic abscesses could produce this picture, but bacterial meningitis or viral encephalitis would have a more rapid course. Subdural or epidural empyema was ruled out by the imaging findings. In Indonesia, tuberculosis is common and must be considered, although the repeated negative smears argued against this diagnosis.

Post-traumatic cerebral contusion or hematoma or carotid-artery dissection would have been symptomatic earlier in the course, and symptoms would likely have been maximal at onset. Traumatic subdural hematoma, in contrast, may have a subacute course but is generally seen in older patients and would have been evident on imaging. Venous-sinus thrombosis, especially in a patient with infection and chronic dehydration, is an essential consideration, but a patient with this condition would be less likely than a patient with bacterial brain abscess to have progressive neurologic findings or these radiographic abnormalities. The clinical setting and imaging findings were not consistent with a vascular malformation or neoplasm.

Finally, demyelinating diseases such as multiple sclerosis or acute demyelinating encephalomyelitis are also theoretically possible. Multiple sclerosis is a common cause of neurologic abnormalities in a

Table 3. Major Entities in the Differential Diagnosis of Hemiparesis in a Young Woman.

Category	Disorder
Infectious	Bacterial brain abscess
	Fungal brain abscess
	Parasitic brain abscess
	Bacterial meningitis
	Viral encephalitis
	Tuberculosis
	Subdural or epidural empyema
Traumatic	Cerebral contusion or hematoma
	Subdural hematoma
	Carotid-artery dissection with infarction
Other disorders	Cerebral venous-sinus thrombosis
	Vascular malformation
	Neoplasm (primary tumor, metastatic tumor, lymphoma)
	Multiple sclerosis
	Acute demyelinating encephalomyelitis
	Sarcoidosis

young woman of northern European heritage, but it is relatively rare in the equatorial nations. Whereas acute demyelinating encephalomyelitis may follow an infectious illness and can occasionally progress over weeks or months, peak deficits usually occur within days of onset.

In this patient, the clinical history, physical findings, and diagnostic-test results were most consistent with a brain abscess.[7] The signs and symptoms of a brain abscess are primarily related to the effects of an expanding intraparenchymal mass, which causes focal neurologic deficits and increased intracranial pressure. Headache (which occurs in 75 percent of patients with an abscess), nausea or vomiting (50 percent), and a change in mental state (50 percent) are common presenting symptoms related to elevated intracranial pressure. Approximately 40 percent of patients present with seizures. Focal deficits, as in this patient, may reflect the location of the abscess, which in turn may be related to the route of spread.[8-10] Hematogenous spread, as appears to have occurred in this patient, generally distributes abscesses at the gray-matter–white-matter junction in locations proportionate to cerebral blood flow, with most deposited in terminal territories of the middle cerebral artery.[11,12] Finally, fever and systemic signs of infection are insensitive markers of central nervous system parenchymal infection, so they are commonly absent with brain abscesses.

The presumptive diagnosis is now primarily made through imaging with contrast-enhanced CT or magnetic resonance imaging. A lumbar puncture is rarely helpful in efforts to isolate an organism, and, as in this case, the cerebrospinal fluid often may not show elevations in protein or cells, particularly for fully encapsulated abscesses. In addition, the risks of herniation because of the mass lesion may preclude a safe lumbar puncture. Stereotactic needle biopsy may be useful for definitive diagnosis and for isolating organisms. In this patient, the diagnosis of brain abscess was supported by radiologic studies. Polymicrobial bacterial invasion of the central nervous system through hematogenous spread was the most probable cause.

The key to treatment for brain abscesses is intravenous antibiotic therapy. Needle-aspiration drainage to reduce mass effect may be necessary, and abscesses that are of fungal origin, multiloculated, resistant, or causing impending herniation may require open excision. The use of corticosteroids is controversial, as these agents may decrease the penetration of antibiotics into the brain and abscess, inhibit encapsulation of the abscess, lower the seizure threshold, and cause side effects. The use of corticosteroids is generally reserved for patients with markedly increased intracranial pressure that causes altered mental status or impending herniation.[11-13] In this patient, corticosteroids were not thought to be necessary. Supportive measures usually include follow-up imaging and seizure prophylaxis as appropriate.

INFECTIOUS COMPLICATIONS OF THE TSUNAMI

Dr. Edward T. Ryan: Two major infectious complications occurred after the tsunami: wound infections and aspiration pneumonia. Wounds were often contaminated with tsunami water, soil, and particulate matter and often were the result of crushing or impaling injuries caused by pieces of wood, rock, concrete, or metal. Even minor wounds and abrasions could rapidly lead to overwhelming infection. Causative agents included staphylococcus and streptococcal species, as well as organisms normally present in water and soil, including vibrio, aeromonas, pseudomonas, burkholderia species, and fungi. Late complications included tetanus.

Tsunami-related aspiration pneumonia was also common. People who survived the wave frequently aspirated not only water, but also soil and particulate matter, as this young woman did. The pneumonic processes that became evident four to six weeks after the initial event were notable for their propensity to cause cavitation, to cause empyema and pneumothorax, and to spread hematogenously, especially to the central nervous system, as in this case. Pneumonia after the aspiration of water or after near-drowning is often polymicrobial, and causative agents that have been reported include aeromonas, pseudomonas, and streptococcus species, oral flora, and others.[14,15] Brain abscesses that complicate chronic pyogenic lung disease, necrotizing pneumonia, and empyemas are well described and are often polymicrobial. A specific association of brain abscesses and pneumonia has been noted with fungi, especially *Pseudallescheria boydii*.[16]

The fact that this patient's aspiration occurred in Southeast Asia raises the possibility of infection with *Burkholderia pseudomallei*, the cause of melioidosis. This aerobic gram-negative rod is a facultative intracellular pathogen, and the soil and water of northern Australia and Southeast Asia, including Indonesia, are areas where the organism is endemic. Infection may result from cutaneous inoculations

or aspiration, and infections range from asymptomatic conditions to overwhelming sepsis. Soft-tissue infections and pneumonia are often necrotizing. Infection with *B. pseudomallei* after near-drowning in Southeast Asia has been reported,[17,18] and pneumonia attributed to this organism has been associated with involvement of the central nervous system, including the formation of brain abscesses.[19]

With no detectable organisms in the sputum, pleural fluid, or cerebrospinal fluid in this patient, we elected to treat her empirically for a probable polymicrobial infection, while addressing the possibility of melioidosis. We used imipenem until the stock of that drug had been exhausted, and then we changed her treatment to vancomycin, ceftazadime, and metronidazole. We also administered vaccines against tetanus and measles and provided her with nutritional support that included multivitamins with vitamin A, zinc, and folate. We recommended that she continue with high-dose intravenous antibiotics for at least six to eight weeks, and then treatment with oral trimethoprim–sulfamethoxazole for at least three to six months, to prevent relapse of infection with *B. pseudomallei*.

A number of infections that could have increased in the region after the tsunami did not. As of the time of our deployment to the area, there had been no major outbreaks of diarrheal illnesses or vector-borne diseases. Their absence was probably due to a confluence of events, including an early emphasis on supplying potable water, successful public health interventions, and at least temporary disruptions of vector-breeding sites. Secondary infectious-disease complications from the tsunami included a possible increase in cases of tuberculosis and other respiratory infections, perhaps related to crowding and destruction of the health infrastructure and public health programs in northern Sumatra.

Dr. Kao: This patient slowly regained coherent speech, then facial movement. She was seen in consultation by the psychiatric service for evaluation and management of post-traumatic stress disorder and depression, and sertraline was started. Over the course of her hospitalization, her affect became visibly brighter, and she became very interactive with the medical staff on the ship. On the day of her discharge, she moved her right leg and arm for the first time and burst into peals of laughter. She was transferred to the International Committee of the Red Cross–Crescent field hospital, where she continued her course of antibiotics and gradually regained movement and strength on her right side, along with the ability to stand and walk independently (Fig. 1B).

Dr. Nancy Lee Harris (Pathology): Captain Llewellyn, do you have any comments from the U.S.N.S. *Mercy*?

Captain Mark Llewellyn, M.D. (Commanding Officer, U.S.N.S. *Mercy*): It was and continues to be an honor and a privilege for us to work alongside our civilian medical counterparts, first for the tsunami relief effort in Banda Aceh, and currently for the earthquake relief effort on Nias Island, Indonesia. Collaborating with Indonesian government and health officials, our international partners and various nongovernmental organizations ashore, our combined team of civilian medical volunteers under Project HOPE, U.S. Public Health Service personnel, civilian mariners of the Military Sealift Command, and U.S. Navy medical and nonmedical personnel truly represented the compassionate heart of the United States.

DIAGNOSIS

Tsunami-related aspiration pneumonia with lung and brain abscesses, probably polymicrobial.

Dr. Cash reports having received grant support from the American Epilepsy Foundation. Dr. Ryan reports having received consulting fees from Raytheon, Acambis, and New England Biolabs–BioHelix. Dr. Ryan holds patents on the following: heterologous antigens in live-cell *Vibrio cholerae* strains; *V. cholerae* proteins expressed during infection; use of the RTX secretion system to achieve heterologous polypeptide secretion by *V. cholerae*.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or U.S. government.

We are indebted to the telemedicine staff of Massachusetts General Hospital and the U.S.N.S. *Mercy*.

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EDITORIALS

Sudden Death after Myocardial Infarction — Who Needs Prophylaxis, and When?

Alfred E. Buxton, M.D.

Although the age-adjusted mortality from cardiovascular disease has declined in recent years, the number of sudden deaths has risen.[1] According to data from the Centers for Disease Control and Prevention, 63 percent of deaths from cardiovascular causes in the United States, or more than 450,000 events, in 1998 were sudden and unexpected, most being attributable to coronary disease. Sudden death is the end result of multiple processes, usually manifested electrocardiographically as ventricular fibrillation or ventricular tachycardia.

The type of arrhythmia observed depends on the temporal relation to myocardial infarction. In the acute phase of myocardial infarction, the metabolic consequences of severe ischemia may trigger ventricular fibrillation, even though ventricular function was often normal before the event. Such cases may account for half of sudden deaths.[2] Scar formation after myocardial infarction may lead to the development of the substrate for intramyocardial reentry, resulting in ventricular tachycardia, which, in turn, may precipitate cardiac arrest in the absence of active ischemia. This type of ventricular tachycardia (usually monomorphic) may develop days or years after the index infarction. Finally, some patients have gradual, extensive ventricular remodeling after myocardial infarction, and the remodeling leads to the syndrome of heart failure. The development of heart failure, with its attendant neurohormonal abnormalities, sets the stage for other mechanisms that may cause ventricular tachycardia (usually the polymorphic type). Thus, the mechanisms responsible for sudden death vary according to their temporal relation to myocardial infarction and multiple other factors, including the presence or severity of left ventricular dysfunction.

In the prethrombolytic era, multiple variables were shown to influence the risk of both sudden and nonsudden death after myocardial infarction. In a substudy of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) reported in this issue of the *Journal*, Solomon and colleagues[3] extend and reinforce our understanding of factors influencing the risk of death after acute myocardial infarction. VALIANT compared the effect of valsartan, captopril, or both on the risk of death in more than 14,000 patients with acute myocardial infarction complicated by left ventricular dysfunction (defined as a left ventricular ejection fraction of 40 percent or less), heart failure, or both between 1998 and 2001.[4] Several characteristics of the patients enrolled in the trial are noteworthy. The mean left ventricular ejection fraction was 35 percent, 28 percent had had a prior myocardial infarction, and approximately three fourths were in Killip class II, III, or IV at the time of enrollment.[4] During a median follow-up of 24.7 months, 7.3 percent of the patients died suddenly or were resuscitated after cardiac arrest.[3] Solomon et al. emphasize two major points: the temporal occurrence of sudden death after myocardial infarction and the importance and limitations of the left ventricular ejection fraction as a risk factor for sudden death.

Clustering of sudden deaths in the early period after myocardial infarction was noted in the prethrombolytic era.[5] The time course of sudden death in the modern era has been explored less extensively, but some work in unselected populations of survivors of acute myocardial infarction suggests a delay in sudden death to 18 months after the acute event.[6] This issue is clarified in the current study. Solomon et al. clearly demonstrate the period of

highest risk to be the first month after myocardial infarction (event rate, 1.4 percent), with a dramatic drop to a fairly constant rate of 0.14 to 0.18 percent per month thereafter.

The association between a reduced left ventricular ejection fraction and an increased risk of death after myocardial infarction has been recognized for years. In both the prethrombolytic era and the post-thrombolytic era, the risk of death increases markedly if the left ventricular ejection fraction is 40 percent or less.[7] At first glance, it may seem surprising that Solomon et al. found the risk of sudden death to be similar among patients with a left ventricular ejection fraction of more than 40 percent and those with an ejection fraction of 30 to 40 percent. This finding is most likely explained by the fact that in order to enter VALIANT, any patient with a left ventricular ejection fraction of more than 40 percent would have had to have heart failure, reaffirming the importance of heart failure as a risk factor for sudden death.

Although Solomon et al. note a number of significant differences between survivors and patients who died, there were no clinically useful factors distinguishing those who died suddenly from those who had a nonsudden death. In other words, a reduced left ventricular ejection fraction and evidence of advanced heart failure carried an equally increased risk of sudden and of nonsudden death and did not have a cause-and-effect relation to arrhythmic events. The importance of this limitation has implications for preventive therapy. If we are to use efficacious treatments, such as implantable cardioverter–defibrillators (ICDs), in a cost-effective manner, we need risk-stratification tests that identify patients whose risk of sudden death significantly exceeds their risk of nonsudden death. To date, there is only one such test — the electrophysiological test.[8]

What is the importance of the current study? It reinforces findings in earlier studies that the risk of sudden death is greatest in the early period after infarction among patients with clinically significant ventricular dysfunction or heart failure. This point raises several questions. Should patients with high-risk characteristics undergo prolonged hospitalization after myocardial infarction? An alternative solution, given the observation of Solomon et al. that risk drops dramatically within six months after acute myocardial infarction, might be to provide noninvasive vest defibrillators or automatic external defibrillators to high-risk patients for limited periods. The latter approach is the subject of an ongoing trial sponsored by the National Heart, Lung, and Blood Institute in selected patients with a recent anterior myocardial infarction. These noninvasive approaches to prophylactic defibrillation are attractive in light of the results of the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), which demonstrated the failure of ICDs to reduce the risk of death among high-risk patients with clinically significant left ventricular dysfunction after a recent myocardial infarction.[9]

How do the results of this large, multicenter trial by Solomon et al. relate to studies demonstrating the ability of ICDs to prevent sudden death in patients with chronic coronary heart disease?[10-12] These trials — the Multicenter Automatic Defibrillator Implantation Trial (MADIT), the Multicenter Unsustained Tachycardia Trial (MUSTT), and MADIT-II — were predicated on earlier observations, similar to those of Solomon et al., that patients with spontaneous ventricular arrhythmias and clinically significant ventricular dysfunction after a recent myocardial infarction have a substantial risk of death. However, a minority of patients in these trials had a myocardial infarction within 2 years before enrollment: the average times from myocardial infarction to enrollment were 39 months in MUSTT and 81 months in MADIT-II. The total mortality rate in VALIANT after the first year was approximately 5 percent per year. The rate of sudden death or resuscitation after cardiac arrest was approximately 2.5 percent per year among patients with a left ventricular ejection fraction of 30 percent or less. After the first year, the total mortality rates and the rate of sudden death were fairly constant and low. These figures contrast with the total mortality rates of 11 percent per year in the control patients with a left ventricular ejection fraction of less than 30 percent in both MUSTT and MADIT-II. Thus, event rates in the ICD trials were double those in VALIANT.

What is the explanation for this difference? In part, it may be due to the fact that two thirds of the patients enrolled in MADIT and MUSTT had symptomatic heart failure, as reflected by a New York Heart Association class of at least II, in addition to a reduced left ventricular ejection fraction. I suspect that another reason for the higher rates of events in the ICD trials is enrollment bias, resulting in the recruitment of patients at very high risk. Why is this important? Because it suggests that the results of the ICD trials may not be generalizable to all pa-

tients meeting the entry criteria for those studies. The mortality risks observed in the ICD trials may have been exaggerated because of the manner in which patients were recruited. Thus, when performing such studies, we must strive to enroll broad-based, representative populations, unencumbered by referral bias.

In summary, the analysis by Solomon et al. is a useful reality check on the problem of sudden death among survivors of acute myocardial infarction. This study documents the natural history of sudden death and some of the risk factors for it with contemporary treatment of myocardial infarction. The challenge going forward is to translate these observations into cost-effective preventive therapy.

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Adjuvant Chemotherapy for Non–Small-Cell Lung Cancer — The Smoke Clears

Katherine M.W. Pisters, M.D.

Lung cancer has been the most common cancer in the world since 1985 and is today the leading cause of cancer-related death. In 2002, there were 1.35 million new cases and 1.18 million related deaths worldwide.[1] Non–small-cell lung cancer, the most common form, accounts for 80 to 85 percent of cases. Given the size of the problem, the benefit of adjuvant chemotherapy for non–small-cell lung cancer, reported by Winton et al. in this issue of the *Journal*, has tremendous implications.[2]

Complete surgical resection is the best hope for cure in patients with operable non–small-cell lung cancer, yet the five-year overall survival rate is only 23 to 67 percent, depending on the size of the primary tumor and the presence or absence of invasion and lymph-node involvement.[3] After surgery, relapse at distant sites occurs two to three times as frequently as local recurrence and is most often fatal. Postoperative radiotherapy decreases the rate of local recurrence in stage IIIA disease but has a detrimental effect on survival in patients with stage I or stage II disease.[4] Adjuvant systemic chemotherapy directed at micrometastatic disease has an established role in the treatment of breast and colon cancer; however, its use in non–small-cell lung cancer has, until now, been controversial.

Decades ago, initial forays into adjuvant therapy for non–small-cell lung cancer failed — the trials were poorly designed and used relatively inactive chemotherapy. The next generation of studies incorporated cisplatin (an agent still considered a cornerstone of treatment), but the studies were too small to detect a benefit.

A 1995 meta-analysis of results from randomized trials of adjuvant therapy conducted between 1965 and 1991 showed that treatment with alkylating agents alone or in combination with radiation reduced overall survival (an absolute decrease in the rate of survival of 5 to 7 percent at five years, and an increase in the risk of death of 15 to 35 per-

cent).[5] Moreover, a cisplatin-based regimen in combination with radiation did not affect overall survival as compared with postoperative radiotherapy alone.[5] The subsequent North American Intergroup (INT 0115) trial, which compared adjuvant etoposide plus cisplatin and radiation with adjuvant radiation alone, confirmed this lack of benefit.[6] However, the 1995 meta-analysis did reveal that cisplatin-based chemotherapy without radiation improved the five-year overall survival rate by 5 percent and reduced the risk of death by 13 percent as compared with no adjuvant therapy.[5] Although this improvement did not achieve statistical significance, it did rekindle interest in postoperative chemotherapy for non–small-cell lung cancer.

The Adjuvant Lung Project Italy (ALPI) trial was the first large study of adjuvant therapy to be reported after the meta-analysis.[7] Among the 1088 patients with completely resected stage I, II, or IIIA non–small-cell lung cancer who could be evaluated and who were randomly assigned to three cycles of mitomycin plus vindesine plus cisplatin or observation, no statistically significant benefit in overall survival was seen with adjuvant therapy. In this study, postoperative radiotherapy was given to 43 percent of patients, 69 percent completed all three chemotherapy cycles, and there were more deaths during the first year in the chemotherapy group than in the observation group. These negative results echoed the findings of earlier trials and again dampened enthusiasm for adjuvant treatment.

The following year, the results of the largest trial of adjuvant chemotherapy for non–small-cell lung cancer reheated the debate.[8] The randomized International Adjuvant Lung Cancer Trial (IALT) included 1867 patients with completely resected stage I, II, or IIIA non–small-cell lung cancer and showed an improvement of 4 percent in the five-year overall survival rate and a reduction of 14 percent in the risk of death after adjuvant chemotherapy with a cisplatin-based two-drug regimen. Postoperative radiotherapy was given to 25 percent of patients, and 74 percent received at least 240 mg of cisplatin per square meter of body-surface area.

Postulated reasons for the contradictory results of the ALPI study and IALT include a larger number of early deaths in the ALPI study and differences in numbers of participants, chemotherapy regimens, and the frequency of postoperative radiotherapy. Although IALT supported the use of adjuvant chemotherapy, patients with lung cancer and physicians were not enthusiastic, given the potential toxic effects of therapy, modest survival benefits, and conflicting results.

Winton and colleagues add considerable fuel to the fire with results that favor adjuvant chemotherapy after complete resection of non–small-cell lung cancer. In their trial (JBR.10), 482 patients with stage IB (T2N0) or stage II (T1N1 or T2N1) non–small-cell lung cancer were randomly assigned to four cycles of adjuvant vinorelbine plus cisplatin or to observation. This is the first trial to treat all patients with a "third generation" chemotherapy agent (vinorelbine), omit postoperative radiotherapy, and focus on a narrow subgroup of patients with operable tumors. All patients began adjuvant therapy within six weeks after surgery and had a performance status score of 0 or 1 (fully ambulatory, minimal symptoms, and good general health). Chemotherapy was not excessively toxic (there were two treatment-related deaths). Compliance with chemotherapy was typical for a trial of adjuvant therapy for non–small-cell lung cancer — 58 percent of patients receiving treatment completed three cycles, and 48 percent completed four cycles of chemotherapy. With a median follow-up of more than five years, the results are astonishing: adjuvant chemotherapy improved the five-year overall survival rate by 15 percentage points as compared with observation alone (69 percent vs. 54 percent, $P=0.03$) and decreased the risk of death by 31 percent ($P=0.04$).

Supportive findings come from Cancer and Leukemia Group B (CALGB).[9] The CALGB protocol 9633 trial included a "modern" chemotherapy regimen (paclitaxel plus carboplatin), omitted postoperative radiotherapy, and focused on an even narrower subgroup of patients (only those with stage IB disease). The 344 patients were randomly assigned to four cycles of adjuvant chemotherapy or observation. Chemotherapy was well tolerated, with no treatment-related deaths and 85 percent of patients completing all planned cycles. The four-year overall survival rate was improved by 12 percentage points in the patients assigned to chemotherapy as compared with those assigned to observation alone (71 percent vs. 59 percent), with a 38 percent decrease in the risk of death. Moreover, the rate of death from lung cancer was reduced by almost half. At this year's annual meeting of the American Society of Clinical Oncology, further evidence of the benefits of adjuvant chemotherapy for non–small-cell lung cancer was presented.[10] The Adjuvant Navelbine International Trialist Association (ANITA) study randomly assigned 840 patients with

completely resected stage IB, stage II, or stage IIIA non–small-cell lung cancer to four cycles of vinorelbine plus cisplatin or to observation. As in the JBR.10 trial, the level of toxic effects was acceptable, and with a median follow-up of more than 70 months, adjuvant chemotherapy increased the 5-year overall survival rate by 8 percentage points (51 percent vs. 43 percent) and decreased the risk of death by 21 percent.

Both the JBR.10 and ANITA trials performed subgroup analyses according to stratification, and neither trial showed a statistically significant survival benefit for patients with stage IB disease. This is in marked contrast to the findings of the CALGB study. These conflicting data may reflect differences in sample size, number of events, or other factors. Furthermore, insufficient numbers of patients with stage IA disease have been studied to allow conclusions to be made about the efficacy of adjuvant therapy in this subgroup. Other encouraging results of adjuvant therapy come from Japan, where investigators have focused on the use of oral uracil–tegafur after resection of non–small-cell lung cancer.[11,12] Although a meta-analysis showed a significant improvement in overall survival among patients treated with uracil–tegafur, as compared with those who did not receive adjuvant therapy,[12] these data have not been confirmed outside of Japan, and the benefits of uracil–tegafur as compared with platinum-based regimens have not been studied.

On the basis of the data reported by Winton et al. and the supporting trials, the controversy surrounding adjuvant chemotherapy for resectable non–small-cell lung cancer is over. Adjuvant platinum-based chemotherapy should be recommended after complete resection of non–small-cell lung cancer in patients with a good performance status. Additional research will enable us to select those patients most likely to benefit from adjuvant therapy, to customize the therapy on the basis of the biology of the tumor, to lessen toxicity and increase compliance, to identify more effective regimens, and to further improve survival.

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Type 1 Diabetes — Does Suppressing T Cells Increase Insulin?

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During the ominous prelude to the onset of type 1 diabetes, the pancreatic-islet beta cells become the targets of a specific autoimmune attack, which ultimately results in diabetes. Although major advances have led to an improved understanding of this disease, important gaps in knowledge must be bridged before insulin replacement is shelved forever. The report by Keymeulen et al.[1] in this issue of the *Journal* is further testimony to how complicated it will be to find a treatment that is superior to insulin alone.

The development of type 1 diabetes may be viewed as a two-step process. In the first step, presumed environmental triggers cause the destruc-

tion of beta cells. It is assumed that pancreatic antigen-presenting cells engulf dead beta cells. The antigen-presenting cells are thought to migrate to lymph nodes that drain the pancreas and in which islet-beta-cell–specific antigen presentation takes place.[2] CD4+ T lymphocytes with T-cell receptors that recognize beta-cell peptides lodged in a groove in the HLA class II molecule may then be activated, which initiates an islet autoimmune reaction.

Islet autoimmunity is best detected with the use of standardized tests for autoantibodies to insulin, IA-2, or glutamic acid decarboxylase (GAD65).[3,4] Autoantibodies can be present in some patients for more than a decade before the onset of diabetes, and it is well documented that these islet autoantibodies, in combination, predict type 1 diabetes.[5]

After autoantibodies have developed, there is a second step, in which genetic as well as environmental factors may aggravate the islet autoimmunity. Perhaps CD8+ cytotoxic T cells are induced, leading to a rapid onslaught on beta cells. Depending on the insulin sensitivity and the age of the patient, hyperglycemia ensues when 80 to 90 percent of beta cells have been destroyed. The older the patient, the more residual beta cells appear to remain at the onset of hyperglycemia. Sadly, the disease process is more aggressive in young children, and type 1 diabetes is being diagnosed at progressively younger ages, even though the total incidence may not be increasing.[6]

The age-dependent clinical onset of type 1 diabetes is also critical in an evaluation of the study by Keymeulen et al. The particular ChAglyCD3 antibody the investigators used is engineered on aglycosylated human IgG1. Only insulin-requiring patients between the ages of 12 and 39 years who had islet-cell antibodies, GAD65 autoantibodies, or both, as well as C-peptide levels greater than 0.20 nmol per liter, were included. The entry criteria ensured that patients with type 1 diabetes who already had had a sizable loss of beta cells at the time of diagnosis did not participate — a factor that was important for reasons discussed below.

Why was an antibody against CD3+ T cells used in a phase 2 clinical trial? Immunosuppressive or immunomodulating agents have been used in an increasing number of clinical studies, since the evidence has been growing that type 1 diabetes is an autoimmune disease. Numerous trials that were either open or poorly controlled were attempted, and in studies during the past 30 years, patients with type 1 diabetes have been exposed to a host of immunosuppressive or immunomodulating agents.[7] Cyclosporine was the first immunosuppressive agent that was used in important placebo-controlled, double-blind clinical trials.[8,9] Beta-cell function was preserved by such an approach, although rarely beyond 12 months. Furthermore, calcineurin nephrotoxicity precluded additional clinical studies.[10]

The ability to predict type 1 diabetes by detecting the presence of islet-cell autoantibodies[3,5] — and the results of studies in laboratory rats and mice with spontaneous diabetes — led to clinical trials of methods to prevent or delay the clinical onset of the disease.[11,12] The administration of parenteral insulin was effective in the prevention of diabetes in the BioBreeding (BB) rat and the nonobese diabetic (NOD) mouse, but the strategy did not prevent the onset of the disease in first-degree relatives of patients with type 1 diabetes who had tested positive for the islet-cell autoantibody.[11] Likewise, although nicotinamide prevented diabetes in the NOD mouse, it was ineffective in a controlled trial in humans.[12]

The study by Keymeulen et al. was based on both experimental animal models and clinical data suggesting that CD3 monoclonal antibodies might affect autoimmune diabetes. Preclinical studies with CD3 monoclonal antibodies were highly effective in the NOD mouse. The study by Keymeulen et al. was also preceded by a placebo-controlled trial in 24 patients with new-onset type 1 diabetes in which another type of humanized CD3 monoclonal antibody was used.[13] The treatment effect on insulin responsiveness lasted for at least 12 months after diagnosis.[13] The mechanisms of action remain unclear, but it is speculated that induction of CD8+ T cells and perhaps so-called regulatory CD4+CD25+ T cells might be of importance.

Two aspects of the present study are particularly important and will have implications for future attempts to treat type 1 diabetes with CD3 monoclonal antibodies or similar agents. The first is safety. Is it an acceptable risk that the ChAglyCD3 antibody was associated with an influenzalike syndrome and symptoms of Epstein–Barr viral mononucleosis? The long-term effects of this treatment and the question of whether the induction of virus-antigen–specific CD8+ T cells was important to the improved beta-cell function must be determined.

Another important aspect of the study by Keymeulen et al. is the finding that the ChAglyCD3 antibody was effective only in a subgroup of pa-

tients — those among the 80 patients who initially had increased residual beta-cell function (at or above the 50th percentile). Studies that have analyzed the age of patients at the onset of type 1 diabetes, the residual beta-cell function, the distribution of HLA genotypes, and autoantibody positivity suggest that the older the patient, the more C peptide is produced at the time of clinical diagnosis and the fewer high-risk HLA genotypes are present.[14] None of these factors appeared to be important in the outcome of the present study, but it is likely that many more teenagers with new-onset diabetes will need to be studied. An additional group that merits further investigation is patients with type 2 diabetes and GAD65 autoantibody, identified as so-called latent autoimmune diabetes in adults.[4]

The fact the ChAglyCD3 antibody appears effective only when substantial function of residual beta cells is present may limit its applicability. On the other hand, the effect of the ChAglyCD3 antibody may signify that a T-cell–dependent destructive process has to be active before a treatment effect is achieved. If the beta-cell killing has gone too far, there is no point in injecting the CD3 monoclonal antibody. Provided that the treatment is safe, it may be reasonable to consider therapy with CD3 monoclonal antibody for patients with a genetic risk of type 1 diabetes who test positive for islet autoantibody. Screening to detect such patients is carried out by the TrialNet network (www.diabetestrialnet.org/hindex.html), sponsored by the National Institutes of Health, and studied in detail in the TEDDY trial (The Environmental Determinants of Diabetes in the Young; www.teddystudy.org).

The demonstration that the ChAglyCD3 antibody was effective primarily in patients with substantial residual beta-cell function suggests that it may be necessary to increase the efficacy of immunotherapy for type 1 diabetes. A recent phase 2 study suggests that the treatment of latent autoimmune diabetes in adults with alum-formulated GAD65 is safe and may also have a beneficial effect on fasting C-peptide levels.[15] If CD3 monoclonal antibodies are shown to be safe, perhaps their use in combination with agents for inducing immune tolerance could lead to improved therapies for type 1 diabetes.

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CLINICAL IMPLICATIONS OF BASIC RESEARCH

How Ebola Virus Infects Cells

Yoshihiro Kawaoka, D.V.M., Ph.D.

Despite its isolation three decades ago, Ebola virus continues to cause periodic outbreaks of severe hemorrhagic fever in humans, and the closely related Marburg virus is responsible for a recent outbreak of disease in Angola. The mortality rate associated with Ebola virus infection can reach 90 percent, and so the prospect of an effective therapy is attractive. A recent study by Chandran et al.[1] sheds light on the molecular events that culminate in infection and may thus lead to a new approach to therapy.

Embedded within the host-derived lipid envelope of Ebola virus are glycoprotein spikes that bind to cells and mediate fusion between the viral envelope and the host cell membrane, enabling the virus to release its contents into the host-cell cytoplasm. Although some viruses, such as paramyxovirus and human immunodeficiency virus (HIV), fuse with the plasma membrane, others — including Ebola virus and influenza viruses — are taken up into the endosome, where they are exposed to a low-pH environment and cross the endosomal membrane to reach the cytoplasm.

Conformational changes must take place in the viral glycoprotein spikes to allow its hydrophobic fusion domain to be inserted into the host cell membrane. These conformational changes serve as a switch that initiates the fusion of the virus to the host cell.

Before Chandran et al.[1] released their findings, only two mechanisms were known to trigger conformational changes in viral fusion proteins. The induction of changes by means of a low pH is exemplified by the hemagglutinin of influenza virus.[2] After binding to the cell surface, influenza virus is internalized by endocytosis. The acidic environment in the endosome induces conformational changes in the viral hemagglutinin, allowing it to mediate fusion between the viral envelope and the endosomal membrane. A different mechanism is illustrated by the envelope glycoprotein 160 (GP160) of HIV, which consists of two domains: a domain that binds the GP120 receptor and a GP41 fusion domain. After GP120 binds to its receptor molecule CD4, it binds to coreceptors such as the chemokine CCR5, triggering a conformational change in the entire protein and enabling GP41 to initiate fusion between the viral envelope and the cell membrane.[3]

Chandran et al.[1] propose a third triggering mechanism (Fig. 1). They discovered that proteolysis by two endosomal cysteine proteases, cathepsin B and cathepsin L (which are active in a low-pH range), renders a conformational change in the surface glycoprotein of Ebola virus. They showed that glycoprotein-mediated infection is substantially reduced in cells lacking these proteases; that cathepsin B and cathepsin L can individually cleave Ebola virus GP1 to yield an approximately 18-kD N-terminal fragment, which is further digested by cathepsin B; that the extent of viral infectivity mediated by glycoprotein is correlated with the efficiency of the production of the 18-kD fragment; and that selective inhibitors of cathepsin B and of both cathepsin B and cathepsin L block viral infection in cultured cells (Fig. 1). Their model therefore predicts that after the internalization of Ebola virus into the endosomes of cells, the C terminus of the viral GP1 is removed by cathepsin B, cathepsin L, or both in the endosome, leaving the 18-kD N-terminal fragment. Subsequent digestion of this fragment by cathepsin B initiates membrane fusion by GP2, the still-intact fusion domain of the glycoprotein molecule.

An experimental vaccine for this disease is now being evaluated,[4] and treatment of experimentally infected nonhuman primates with a recombinant inhibitor of factor VIIa or tissue factor yields a 33 percent survival rate under conditions that are lethal to nearly all nontreated animals.[5] Despite these encouraging results, there still are no antiviral drugs (not even experimental ones) available for clinical use. The findings of Chandran et al.[1] are therefore notable not only from a basic-science perspective, but also from other perspectives, because they point to a new direction in the treatment of this infection. Although the cathepsin inhibitors used in this study

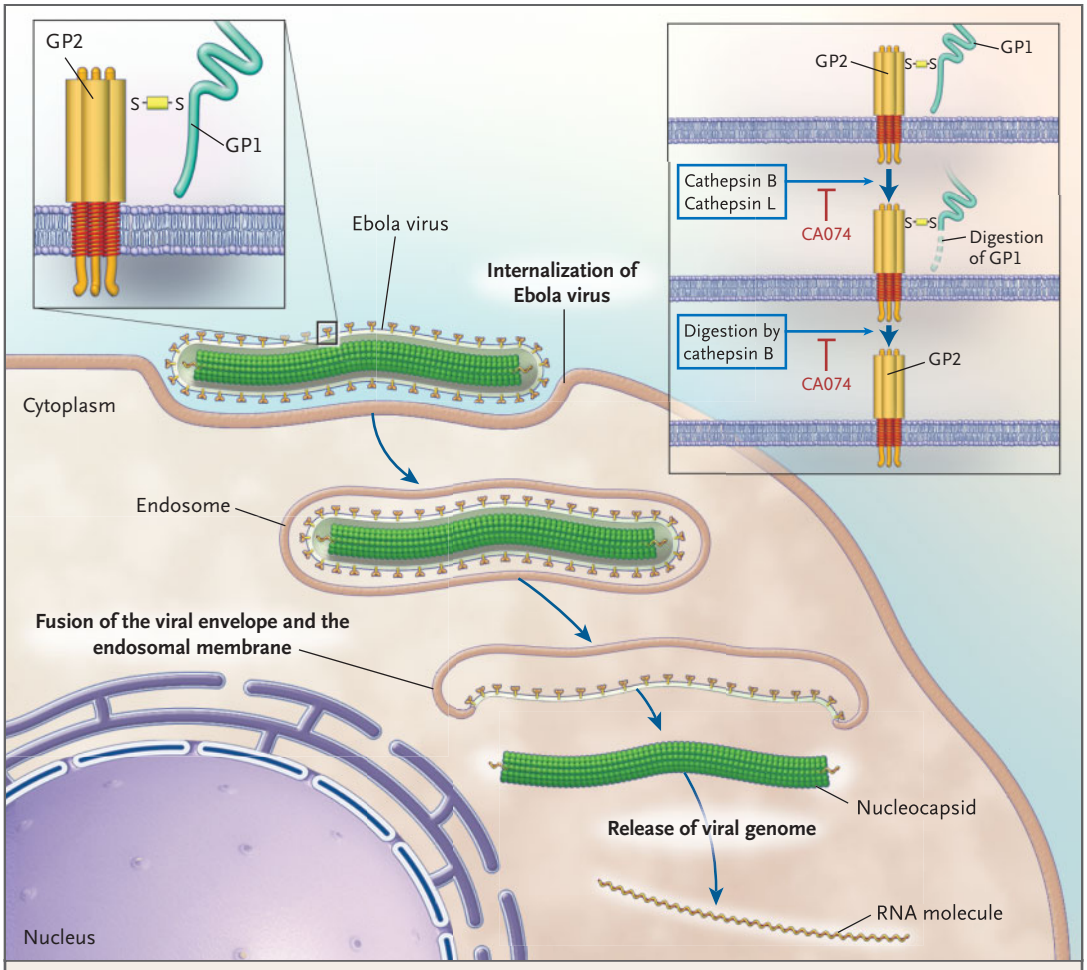

Figure 1. Entry of Ebola Virus into a Cell.

On binding to cell-surface receptors, Ebola virus is internalized and sequestered within an endosome. A recent study by Chandran and colleagues[1] shows that two endosomal proteases, cathepsin B and cathepsin L, then cleave the viral glycoprotein 1 (GP1) to yield a short N-terminal fragment, which is further digested by cathepsin B, leaving only GP2. Presumably, GP2 initiates fusion between the viral envelope and the endosomal membrane, leading to the release of the viral genome into the cytoplasm. A selective inhibitor of cathepsin B, CA074, inhibits the proteolysis of GP1, thereby preventing fusion and thus infection.

are toxic to cells and are therefore unlikely to be used in clinical settings, the development of new types of cathepsin inhibitors that might safely block the replication of Ebola virus in humans may offer a means of controlling this deadly infection.

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CORRESPONDENCE

Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction

TO THE EDITOR: Sabatine et al. (March 24 issue)[1] demonstrated in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 trial that clopidogrel added to aspirin, heparin, and thrombolytic therapy for myocardial infarction with ST-segment elevation reduced the composite end point of TIMI grade 0 or 1 flow, death from any cause, or recurrent myocardial infarction. However, the benefit in terms of this composite end point was driven by the greater TIMI flow grade achieved in the clopidogrel group than in the placebo group; there were no differences between the groups in the rates of the clinical end points of death and of recurrent myocardial infarction. Previous trials comparing reteplase with alteplase showed that better TIMI flow grades were achieved with reteplase than with alteplase, but there was no reduction in mortality with reteplase.[2,3] Tenecteplase was associated with TIMI flow grades that were similar to those found with alteplase and also resulted in no difference in mortality.[4,5]

These conflicting results suggest that a higher TIMI flow grade is not necessarily equivalent to greater clinical and survival benefits. Previous studies of antiplatelet agents in myocardial infarction relied on clinical, rather than surrogate, outcomes. More relevant clinical end points, rather than angiographic outcomes, are needed before clopidogrel is adopted as routine adjunctive therapy with thrombolysis.

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THE AUTHORS REPLY: Chua and colleagues comment that the difference between the clopidogrel and pla-

THIS WEEK'S LETTERS

cebo groups in the rate of the primary end point was driven primarily by differences in the patency of the infarct-related artery. This should not be surprising, since our trial was designed to test whether clopidogrel would improve patency.[1] As we stated, death or myocardial infarction before angiography was included as a necessary surrogate for failed reperfusion or reocclusion. Multiple studies have validated the association between the TIMI flow grade and clinical outcomes.[2,3] To that end, in CLARITY–TIMI 28 we demonstrated that clopidogrel not only improved patency, but also significantly reduced the odds of death from cardiovascular causes, recurrent myocardial infarction, or urgent revascularization through 30 days. Furthermore, we direct the attention of Chua and colleagues to the results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study 2,[4] which were presented alongside those of CLARITY–TIMI 28 findings and which showed that in nearly 46,000 patients with acute myocardial infarction, the addition of clopidogrel resulted in a significant, 7 percent reduction in mortality.[5] Thus, the angiographic and clinical data are quite consistent in indicating that clopidogrel improves the rate of patency of the infarct-related artery and reduces the rate of adverse clinical events, including death.

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Cardiovascular Risk Associated with Celecoxib

TO THE EDITOR: Solomon et al., for the Adenoma Prevention with Celecoxib (APC) Study Investigators (March 17 issue),[1] reported an increase in cardiovascular events associated with the use of celecoxib, and two accompanying editorials[2,3] supported the conclusion of a class effect for cyclooxygenase-2 (COX-2) inhibitors. Although abundant and concordant data from both randomized trials and observational studies show that the use of rofecoxib is associated with cardiovascular risk, the literature concerning the risk with the use of celecoxib is more heterogeneous. Numerous observational studies[4-8] have failed to identify an increased risk with celecoxib. Moreover, among randomized trials of celecoxib with a minimum of 12 months of follow-up, the totality of the evidence of an increased cardiovascular risk is again far from conclusive (Fig. 1, facing page). Caution in prescribing any COX-2 inhibitor, including celecoxib, is mandatory, but publication of the results of the APC trial without insistence on a more thorough discussion of other, similar trials may present a biased picture. Although an increased cardiovascular risk associated with the use of celecoxib is certainly possible, particularly in the incompletely studied high-risk population, this risk has not been established with the conviction implied in the *Journal.*

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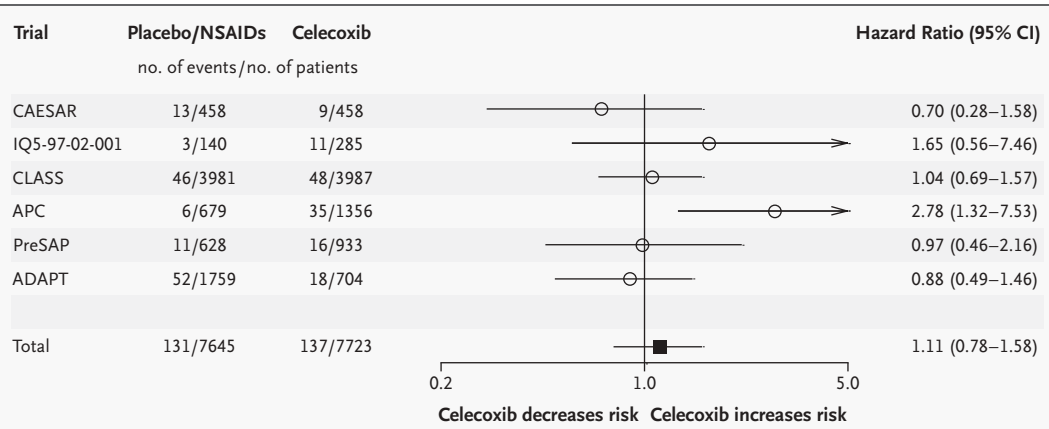

Figure 1. Risk of Cardiovascular Events Associated with the Use of Celecoxib, Placebo, or Traditional Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Trials with Follow-up of at Least 12 Months.

Open circles and the black square denote hazard ratios, and horizontal lines 95 percent confidence intervals (CI). Data are from the Food and Drug Administration hearings of February 16 to 18, 2005 (www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4090M1_Final.htm, accessed June 2, 2005), with the exception of the Alzheimer's Disease Antiinflammatory Prevention Trial (ADAPT) data, which are based on an extrapolation from newspaper articles. CAESAR denotes Canada, Australia, Europe, South Africa trial; IQ5-97-02-001 Double-Blind, Randomized, Placebo-Controlled, Comparative Study of Celecoxib for the Inhibition of Progression of Alzheimer's Disease; CLASS Celecoxib Long Term Arthritis Safety Study trial, APC Adenoma Prevention with Celecoxib study; and PreSAP Prevention of Spontaneous Adenomatous Polyps trial.

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THE AUTHORS REPLY: Most data on the cardiovascular risk associated with celecoxib have come from observational studies or short-term randomized trials. Discrepant findings between observational studies and randomized trials[1-3] underscore the potential limitations of observational data. A modest "signal" of harm may also be obscured by misclassification of end points that are not carefully adjudicated. The heterogeneity of the trials analyzed by Dr. Brophy — including differences in study design, populations, length of follow-up, dosing, and ascertainment of outcomes — makes interpretation of these results challenging. Only three studies cited by Dr. Brophy were placebo-controlled — APC, PreSAP, and IQ5-97-02-001 — and all showed hazard ratios above 1 (the data presented for PreSAP were preliminary). The conclusions of our study were tempered by the small number of events and wide confidence intervals; however, the internal consistency of the data — increased hazards for all cardiovascular end points and a dose–response relationship — along with similar findings from trials of other drugs in this class support our conclusions. Moreover, a consistent safety concern should not require the same degree of statistical conviction as a proof of benefit.

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THE EDITORIALISTS REPLY: We agree that the literature concerning celecoxib is heterogeneous. One

source of the heterogeneity is discrepancies in the numbers of events reported for celecoxib across various versions of the same trial. For instance, the original CLASS trial publication included only the first six months of events.[1] Brophy's figure lists 46 and 48 events for one year; but the report by White and colleagues lists 49 and 52 events.[2] In the Alzheimer's study (IQ5-97-02-001), celecoxib is weakly associated with an increase in cardiovascular risk (odds ratio, 1.65; 95 percent confidence interval, 0.56 to 7.46), but the unpublished report indicates that "a statistically significant difference favoring placebo in adverse events was observed for certain cardiovascular-risk–related body system terms."[3] Events in some but not all of the trials were adjudicated by independent committees. Brophy's analysis pools two different comparison groups, users of nonsteroidal antiinflammatory drugs and placebo groups. Timely publication and full reporting of events would have enabled physicians and scientists to adequately assess the risks associated with celecoxib.

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Morphine, Gabapentin, or Their Combination for Neuropathic Pain

TO THE EDITOR: The cleverly designed and carefully conducted crossover trial reported by Gilron et al. (March 31 issue)[1] shows better control of neuropathic pain with the combination of morphine and gabapentin than with single agents or placebo. Although we admire the meticulousness of the investigators, we also marvel at the unusually rigid adherence of the majority of the patients to a demanding and complex drug regimen. We must conclude that this was a very select group of highly motivated and fastidious patients. It is likely that they had many more personality traits in common with one another than with the general population.

Given that an improvement in mood is associated with a reduction in the perception of pain severity, a finding again replicated in this study, it is likely that the response to any drug therapy is highly dependent on personality. This leads us to question whether this result can be applied to the rest of patients who have neuropathic pain. Further studies are needed to determine the effectiveness of this combination in clinical practice.

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1. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324-34.

TO THE EDITOR: Gilron et al. report the superior efficacy of gabapentin and morphine combined in relieving neuropathic pain. Additional information might further elucidate their important findings.

First, was the neurologic assessment scored to fulfill minimal criteria for the diagnosis of diabetic peripheral neuropathy?[1,2] In elderly patients, decreased or absent ankle reflexes alone are not diagnostic of neuropathy.[3] Were peripheral pulses assessed, since peripheral vascular disease, which is common in diabetes, is associated with pain? Also, since glycemic control influences the intensity of pain, were additional measurements of glycosylated hemoglobin performed over the five months of the study?

Second, we were surprised that 40 percent of the patients with diabetes had not had any pain-relieving drugs prescribed previously. If these patients had milder pain, could this have influenced the results? Is first-line use of combination treatment in such cases necessary?

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Dr. Tesfaye reports having received consulting fees from Pfizer.

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THE AUTHORS REPLY: The detailed neurologic assessments that were performed in patients who were being evaluated for this trial were not scored. These patients were screened by means of a detailed interview and review of all available medical records, a physical examination (including, but not limited to, neurologic and cardiovascular examinations — with routine assessment of peripheral pulses), and laboratory or special tests, or both, that were necessary to confirm the diagnosis of postherpetic neuralgia or of distal, symmetric, sensory diabetic polyneuropathy, and among patients with diabetic neuropathy, to rule out other nutritional, endocrine, toxic, and immune-mediated causes.[1] There were no patients enrolled in the trial with decreased or absent ankle reflexes as the only abnormal neurologic finding. Measurements of glycosylated hemoglobin were not repeated after the trial had begun.

We, too, were unpleasantly surprised by the degree of undertreatment of pain among our patients. Data from a patient survey by our group support this observation, which we have recently discussed.[2] The mean score for baseline pain intensity ranged from 5.6 to 5.8 on a scale from 0 to 10, indicating at least moderate pain (a score above 4) in almost all patients. Therefore, the apparently high degree of undertreatment was not a reflection of milder pain among our study patients.

In the setting of chronic pain, patients' compliance with treatment is generally higher than in that of other conditions (e.g., hypertension), where symptomatic improvement is not readily appreciated.[3] Thus, greater compliance may also be expected in analgesic trials. Furthermore, the rate of withdrawal from our trial was similar to dropout rates in previous studies of similar complexity and duration.[4] Nevertheless, the generalizability of trial results to broader populations and diverse treatment settings is never implicit, and research findings must be viewed from a clinical perspective when treatment is being individualized. With regard to combination analgesic therapy, the anticipated benefits of polypharmacy need to be weighed against possible problems, such as the increased risk of medication errors, decreased compliance, and the potential for adverse drug interactions.[5] With these issues taken into consideration, this study provides evidence in support of the benefit of combining gabapentin and morphine for neuropathic pain.

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1. Diabetic polyneuropathy in controlled clinical trials: consensus report of the Peripheral Nerve Society. Ann Neurol 1995;38:478-82.
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Blast Injuries

TO THE EDITOR: DePalma et al. (March 31 issue)[1] review four patterns of injuries from explosions and offer protocol for evaluating blast injuries that is based on the presence or absence of ruptured tympanic membranes. However, as suggested in the article, tympanic-membrane perforations are found in only 60 percent of patients with clinically significant injuries, and clinically significant injuries are present in less than 30 percent of patients with tympanic-membrane perforations.[2,3]

We summarize our findings from our experience with more than 30 mass-casualty incidents caused by terrorist bombing. First, most persons with clinically significant blast-associated lung injury have respiratory failure within minutes after the explosion. Among those few who have delayed respiratory failure, additional features are manifested in the primary evaluation, such as dyspnea and hemoptysis. Relying on tympanic-membrane perforation and a screening chest radiograph is unnecessary. Second, patients in stable condition — with or without tympanic-membrane perforation — who do not have hemoptysis or tachypnea and in whom the primary evaluation reveals no evidence of other clinically significant injuries may be discharged if vital signs are stable after four to six hours of obser-

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THE AUTHORS REPLY: The detailed neurologic assessments that were performed in patients who were being evaluated for this trial were not scored. These patients were screened by means of a detailed interview and review of all available medical records, a physical examination (including, but not limited to, neurologic and cardiovascular examinations — with routine assessment of peripheral pulses), and laboratory or special tests, or both, that were necessary to confirm the diagnosis of postherpetic neuralgia or of distal, symmetric, sensory diabetic polyneuropathy, and among patients with diabetic neuropathy, to rule out other nutritional, endocrine, toxic, and immune-mediated causes.[1] There were no patients enrolled in the trial with decreased or absent ankle reflexes as the only abnormal neurologic finding. Measurements of glycosylated hemoglobin were not repeated after the trial had begun.

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Blast Injuries

TO THE EDITOR: DePalma et al. (March 31 issue)[1] review four patterns of injuries from explosions and offer protocol for evaluating blast injuries that is based on the presence or absence of ruptured tympanic membranes. However, as suggested in the article, tympanic-membrane perforations are found in only 60 percent of patients with clinically significant injuries, and clinically significant injuries are present in less than 30 percent of patients with tympanic-membrane perforations.[2,3]

We summarize our findings from our experience with more than 30 mass-casualty incidents caused by terrorist bombing. First, most persons with clinically significant blast-associated lung injury have respiratory failure within minutes after the explosion. Among those few who have delayed respiratory failure, additional features are manifested in the primary evaluation, such as dyspnea and hemoptysis. Relying on tympanic-membrane perforation and a screening chest radiograph is unnecessary. Second, patients in stable condition — with or without tympanic-membrane perforation — who do not have hemoptysis or tachypnea and in whom the primary evaluation reveals no evidence of other clinically significant injuries may be discharged if vital signs are stable after four to six hours of obser-

vation. Finally, multiple penetrating wounds from metallic fragments are common, creating diagnostic and treatment difficulties, especially in persons in unstable condition. If blood is present in the trachea, we consider blast-associated lung injury to be the primary cause of instability and treat the condition accordingly. However, if the patient has no response to treatment or if blood is not present in the trachea, penetrating trauma should be considered as the cause of instability.

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TO THE EDITOR: Current explosive devices are particularly challenging in that they are often loaded with metallic objects to inflict penetrating injuries in crowded civilian settings. The Israel National Center for Trauma and Emergency Medicine Research manages the Israeli National Trauma Registry and has accumulated data in the past four years on the nature and consequences of these new injuries and the challenges they present for caregivers. The registry has data on 976 people who have been injured by explosions. Explosives detonated by suicide bombers frequently included nails, bolts, and other metal parts, often referred to as shrapnel. Detonation in crowded and confined spaces increased the effects of the explosions. Nearly 30 percent of hospitalized patients had injuries that were categorized as severe to critical (injury-severity score, ≥16). Triage has changed, since shrapnel, nails, and bolts contained in the bombs penetrate the body with great force and may result in tiny holes that are easily hidden by hair or clothes. Among casualties of explosive devices set off by suicide bombers, 37 percent of patients underwent computed tomographic scanning and 26 percent underwent ultrasonographic scanning in the emergency department; others underwent total-body fluoroscopy in the operating room. From the emergency department, 28 percent of the patients went directly to the operating room, 10 percent to the intensive care unit, and only 58 percent directly to the ward (approximately 3 percent were unaccounted for). The injuries were mainly internal injuries, open wounds, and burns, with an excess of injuries to nerves and to blood vessels as compared with other trauma situations. Some patients had multiple complex injuries that called for contradictory treatment protocols. These findings have implications for triage, diagnosis, treatment, hospital organization, and the definition of surge capacity.

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TO THE EDITOR: The Kleihauer–Betke assay does not test for maternal hemorrhage, as stated in the article by DePalma et al. on blast injuries. Instead, it is a test for the presence of fetal red cells in the maternal circulation.[1] Although small numbers of fetal cells can be detected in the maternal circulation throughout gestation, large numbers of fetal red cells in the maternal circulation are diagnostic of fetal–maternal hemorrhage, as with placental abruption. Pregnant women who have sustained abdominal trauma from any cause and who have a positive Kleihauer–Betke test should receive Rh immune globulin to prevent Rh isoimmunization if they are Rh-negative and unsensitized.

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THE AUTHORS REPLY: We thank Dr. Barham for his clarification regarding the Kleihauer–Betke assay.

The clinical experience of our Israeli colleagues and the importance of the Israeli National Trauma Registry in documenting the nature, severity, and outcomes of injuries from terrorist bomb explosions

cannot be overemphasized. The schema of tympanic-membrane evaluation was offered as a tool for a limited subgroup of persons involved in mass-casualty situations who have been spared fragment injuries but might have sustained a blast injury. We agree that patients who incur pulmonary injuries from a blast, particularly in a confined space, will have immediate symptoms.

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Boxed Warning Added to Promethazine Labeling for Pediatric Use

TO THE EDITOR: In late 2004, a "boxed warning" was added to the labeling for promethazine hydrochloride (Phenergan), including a contraindication for use in children less than two years of age and a strengthened warning with regard to use in children two years of age or older. We describe the basis for this action.

Promethazine is widely used in children as an antihistamine, antiemetic, and sedative. Since its approval in 1951, serious and often life-threatening adverse events, including respiratory depression, oversedation, agitation, hallucinations, seizures, and dystonic reactions, have been reported with promethazine use in children.[1,2] The occurrence of these adverse events, particularly respiratory depression reported when promethazine was used in combination with other drugs that themselves may cause respiratory depression, led the American Academy of Pediatrics in 1995 to reappraise the use of promethazine in combination with other drugs and to discourage the use of promethazine as anesthetic premedication.[3]

In 2000, the warnings section of the label was strengthened to recommend that promethazine not be used in children younger than two years of age and that it be used with caution in children two years of age or older because of the potential for fatal respiratory depression. Despite these labeling changes, the Food and Drug Administration (FDA) continued to receive reports of life-threatening and fatal respiratory depression in young children. In 2004, we reviewed all cases of serious adverse events reported to the FDA that involved children (age range, birth to 16 years) who had received any formulation of promethazine. Reports on adverse events in 125 patients were submitted between 1969 and 2003. The adverse events included 38 cases of respiratory depression, apnea, or cardiac arrest; 29 cases of extrapyramidal dystonic reactions; 24 cases of other central nervous system reactions; 15 cases of seizures or seizure-like activity; 12 cases of dermatologic reactions, and 5 cases of the neuroleptic malignant syndrome. These reports to the FDA included respiratory depression in 22 patients who were 1.5 months to 2 years of age, 7 of whom died. Nine of these 22 patients received 1 mg or less of promethazine per kilogram of body weight, plus another drug with respiratory depressant effects. A wide range of weight-based doses (0.45 to 6.4 mg per kilogram) was associated with respiratory depression. Serious outcomes, including death, disability, life-threatening events, and hospitalization, occurred with all routes of administration (oral, rectal, and parenteral).

We determined that the unpredictable nature of the adverse events and their serious outcomes justified further strengthening of warnings and contraindications and the addition of a boxed warning for the use of promethazine in children.[4]

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1. Hickson GB, Altemeier WA, Clayton EW. Should promethazine in liquid form be available without prescription? Pediatrics 1990;86:221-5.
2. Cote CJ, Karl HW, Notterman DA, Weinberg JA, McCloskey C. Adverse sedation events in pediatrics: analysis of medications used for sedation. Pediatrics 2000;106:633-44.
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Treatment of Survivors after the Tsunami

TO THE EDITOR: The tsunami that struck the Asian subcontinent and Africa on December 26, 2004, caused the deaths of more than 200,000 people. In Thailand more than 10,000 people were treated in ambulatory health centers. After a tsunami, the effects on people occur in three phases. The injuries that are incompatible with life (e.g., severe cardiovascular events, head injury, and blunt injury) happen in the first minutes; then, over the following hours, complications such as massive hemorrhage, hemopneumothorax, and pulmonary embolism are seen. These are followed, in turn, by the late complications, including infectious diseases that develop over days to weeks.[1]

A tsunami directly injures the victims by the mechanism of blunt trauma and penetrating injury to any part of the body.[1] Soil, small pieces of wood, and glass in the contaminated saltwater penetrate the soft tissue of victims at high velocity. Most of those who survived the disaster also had saltwater aspiration. In most of those admitted to health care facilities with cellulitis, progressive fasciitis developed unless there was prompt treatment with appropriate antibiotics and aggressive débridement.[2] Other common complications included bony fractures, soft-tissue contusions, hypoxic encephalopathy, and acute stress disorder.

The volunteer medical team at Rajavithi Hospital in Bangkok, Thailand, treated 37 patients with serious medical complications. All 37 had aspirated saltwater contaminated with soil and had soft-tissue infections. Aspiration pneumonia (in 17 patients), pneumothorax (in 7), and pneumomediastinum (in 3) were the major respiratory problems. In eight patients the acute respiratory distress syndrome developed, with a progressive course in three, rapid resolution followed by severe pneumonia in three, and rapid resolution followed by mild-to-moderate pneumonia in two.

Burkholderia pseudomallei is endemic in this region.[3] We encountered one human immunodeficiency virus (HIV)–positive patient with a *B. pseudomallei* lung abscess and one patient with diabetes mellitus in whom acute *B. pseudomallei* lobar pneumonia developed (Fig. 1). Table 1 summarizes the clinical findings in these two patients, who had melioidosis after the disaster. Both were febrile, with cough, dyspnea, and sputum production, and required respiratory support.

Among all the patients, cultures of blood, sputum, or pus contained the following organisms: *Pseudomonas aeruginosa* (in four patients), *B. pseudomallei* (in two), *Stenotrophomonas maltophilia* (in one), *Acinetobacter baumanii* (in five), *Escherichia coli* (in three), klebsiella (in three), enterobacter (in two), neisseria (in one), citrobacter (in one), corynebacteria (in two), and viridans streptococcus (in two). All the patients were treated with combination antibiotic therapy (imipenem plus cotrimoxazole [trimethoprim–sulfamethoxazole]) that is active against pseudomonas and *B. pseudomallei*.

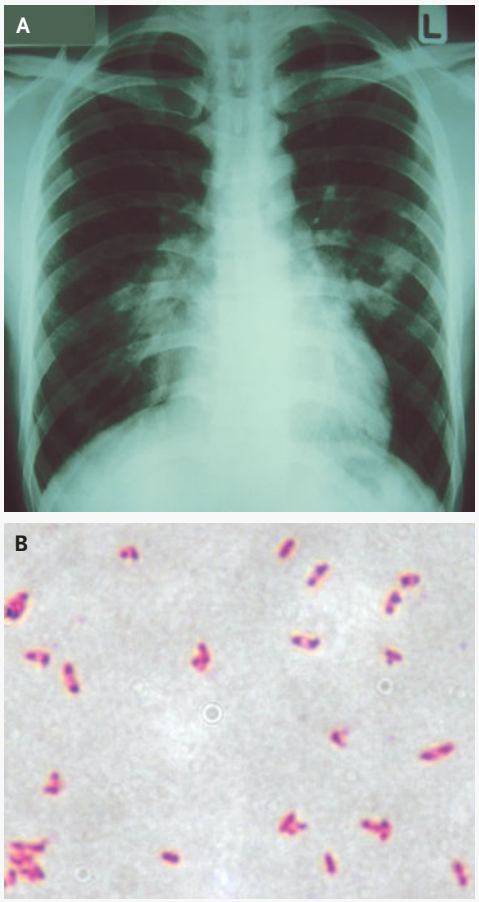

Figure 1. *B. pseudomallei* Lung Abscess in a Patient after the Tsunami.

Panel A shows a radiograph of the chest, obtained eight days after the aspiration of soil-contaminated saltwater in a patient with an acute *B. pseudomallei* lung abscess of the left middle lung zone. Gram's staining of sputum for *B. pseudomallei* (Panel B) shows the "safety-pin" appearance (bipolar staining appearance) of these gram-negative rods.

Table 1. Clinical Findings in Two Patients with *B. pseudomallei* Infection and Melioidosis after the Tsunami.*

Characteristic	Patient 1	Patient 2
Age (yr)	24	64
Underlying condition	HIV infection	Diabetes mellitus
History and findings	Aspiration of soil-contaminated saltwater; fever, chest pain and dyspnea, hemoptysis	Aspiration of soil-contaminated saltwater; fever and severe dyspnea with alteration of consciousness; 6-cm laceration on left leg
Days to onset of pneumonia	7	3
Clinical manifestation	Aspiration pneumonia	Aspiration pneumonia with respiratory failure
Leukocyte count (per mm^3)	22,700	13,300
Neutrophil count (%)	74	89
Ventilatory support	Oxygen by nasal cannula; maximum FiO_2, 0.36	Intubation with mechanical ventilation; maximum FiO_2, 0.99
Specific antibiotic treatment	Imipenem for 10 days, then oral cotrimoxazole (trimethoprim–sulfamethoxazole) added	Imipenem for 8 days, then oral cotrimoxazole (trimethoprim–sulfamethoxazole) added
Related complications	*B. pseudomallei* lung abscess	*B. pseudomallei* septic shock; hyperglycemia

* FiO_2 denotes fraction of inspired oxygen.

In summary, the tsunami hit in an area where *B. pseudomallei* is endemic,[3-5] and the patients needed treatment for *B. pseudomallei* and also treatment with antibiotics that are active against anaerobic bacteria, débridement, and respiratory care.

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BOOK REVIEWS

RADIOLOGIC–PATHOLOGIC CORRELATIONS FROM HEAD TO TOE: UNDERSTANDING THE MANIFESTATIONS OF DISEASE

Edited by Nicholas C. Gourtsoyiannis and Pablo R. Ros.
797 pp., illustrated. Berlin, Springer-Verlag, 2005.
$350. ISBN 3-540-04395-0.

THIS UNIQUE BOOK IS THE FIRST SERIOUS attempt to correlate state-of-the-art radiologic images of the entire body with the underlying pathology. The contributors include recognized investigators in 12 European countries and the United States. The book was based on a categorical course presented for many years at the European Congress of Radiology. It covers key aspects of disease from head to toe by showing the correlation of modern imaging techniques with microscopic and gross pathology. Although much clinical material is available on radiologic–pathological correlation, this is the first comprehensive textbook to offer it in a single source — a collection of topics on the entire body merged with state-of-the-art images. The book shows that neoplasms are a logical starting point for radiologic–pathological correlation, because they are frequently resected in toto and offer the basis for superb comparisons of gross-anatomical imaging.

The nidus of the development and presentation of radiologic–pathological correlation was the establishment in 1947 of the Department of Radiologic Pathology and its Registry at the Armed Forces Institute of Pathology in Washington, D.C. Many recognized national and international congresses have sponsored successful courses in radiologic–pathological correlation, including the European Congress of Radiology, the International Congress of Radiology, the Radiological Society of North America, and other subspecialty societies. This approach has become a primary teaching tool for understanding radiologic manifestations of disease, from plain radiographs to the cross-sectional imaging techniques of x-ray computed tomography, magnetic resonance imaging, positron-emission tomography, single-photon emission tomography, and ultrasonography. For many decades now, the teaching of radiologic principles has continued to gain strength, by providing radiologic–pathological correlation as a demonstration beyond the "what" of radiology to the "why" and "how" of radiologic findings. In current radiology residencies, the need for radiologic–pathological correlation continues, but in reality it is losing momentum, owing to the decrease in the frequency of autopsies, which decreases the quantity and quality of pathological material for possible radiologic–pathological correlation. This textbook, therefore, fills this gap by providing the correlation in an environment in which there is, ironically, a decreasing volume of pathological material.

This book realizes the goal of the editors: to provide radiologists, pathologists, and other specialists with a single source that presents the state of the art in the educational technique of radiologic–pathological correlation. The authors have, in many cases, dedicated their entire professional lives to teaching young radiologists around the world to use this technique. Many of the U.S. and European authors have direct or indirect links with the Armed Forces Institute of Pathology, having served there as full-time faculty, distinguished lecturers, or researchers in radiologic–pathological correlation.

The book is divided along main-organ-system lines, including neuroradiology, head and neck, chest, abdominal–gastrointestinal, urogenital, musculoskeletal, and breast imaging. The discussion of each organ system is systematic and often involves the study of benign and malignant neoplasms. The book should serve as an effective reference for the evaluation of difficult cases by practicing radiologists, and it should also help trainees in radiology to attain a thorough knowledge of the pathological basis of disease. The editors have successfully orchestrated the contributions of multiple international authors, teachers, and investigators to produce a compendium of high-resolution images obtained by multiple methods and color prints of gross pathology and histology. The book should become required reading for teachers and students in radiology, pathology, and associated disciplines.

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CANCER OF THE SKIN

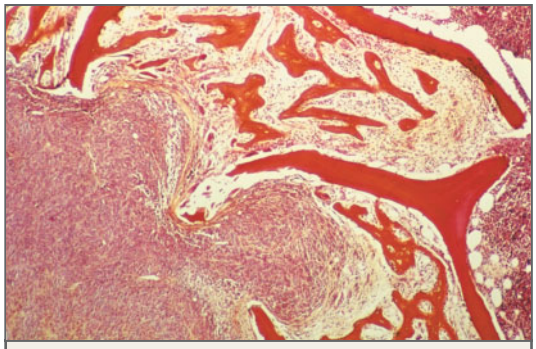
Edited by Darrell S. Rigel, Robert J. Friedman, Leonard M. Dzubow, Douglas S. Reintgen, Jean-Claude Bystryn, and Robin Marks. 711 pp., illustrated, with CD-ROM. Philadelphia, Saunders, 2005. $179. ISBN 0-7216-0544-3.

Despite advances in the diagnosis, treatment, and understanding of the causes of skin cancer, the incidence of cutaneous neoplasms continues to increase: there were more than 1.3 million reported cases in the United States in 2004. It is now estimated that a cutaneous neoplasm will develop in one in five persons born in the United States. Although the overwhelming majority of these neoplasms are basal-cell carcinomas and squamous-cell carcinomas, there were almost 60,000 cases of melanoma this past year.

Considering the scope of the problem, relatively few textbooks deal with the entire spectrum of cancers of the skin. This excellent book, which updates the edition published more than a decade ago, fills that void. The editors have assembled an impressive array of leading experts in cutaneous oncology to write the chapters. This effort has resulted in a complete collection of the most up-to-date and relevant information regarding the diagnosis and management of skin cancer currently available in one source.

The organization of the book is useful and logical. The book begins with an analysis of the cell biology, genetics, epidemiology, and etiology of skin cancers and then moves on to an assessment of basal-cell carcinoma and squamous-cell carcinoma, the two most common tumors of the skin. The detailed examination of one of the most lethal cutaneous malignant diseases, melanoma, is thorough and will be of great practical value to the clinician. The second half of the book reviews the less common cutaneous neoplasms, such as Merkel-cell carcinoma and dermatofibrosarcoma protuberans. The last section covers the range of treatments in cutaneous oncology.

This comprehensive and authoritative work is easy to read. Throughout, the text is supported by ample full-color clinical photographs and many informative tables and graphs in full color. The extensive use of color images is a substantial improvement over the previous edition. This edition also details numerous advances in cutaneous oncology, such as the use of topical immunomodulators and photodynamic therapy. Although the focus is primarily on the recognition and management of primary tumors of the skin, the book also considers such topics as sentinel-lymph-node biopsy (for melanoma) and radiation therapy, which are often omitted from traditional dermatologic textbooks.



Photomicrograph of Skin Tissue Showing Melanoma.

Ida Wyman/Phototake.

This book is an excellent primary resource for any physician seeking reliable and accessible information on cancer of the skin. It will also serve as a valuable ancillary resource for practitioners whose clinical duties involve the management of skin cancer, because it provides a thorough understanding of the biologic behavior, clinical presentation, and current treatment of malignant diseases of the skin.

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MEDICAL MANAGEMENT OF KIDNEY TRANSPLANTATION

Edited by Matthew R. Weir. 561 pp., illustrated. Philadelphia, Lippincott Williams & Wilkins, 2005. $129. ISBN 0-7817-4491-1.

Transplantation has been a miracle of modern medicine. The success of transplantation of all solid organs began with the pioneers of kidney transplantation, who developed, tested, and refined innovative immunosuppressive treatment. In the early years, the American transplantation group consisted of a small number of transplantation surgeons who met annually at the Drake Hotel in Chicago. Over the past three decades, the American Transplant Congress has outgrown Chicago and many other sites for its meetings. The

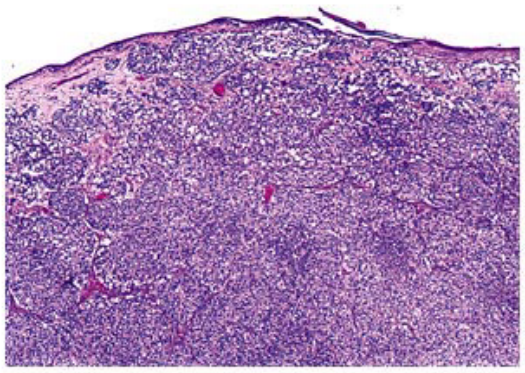
CORRECTION

Cancer of the Skin

Cancer of the Skin . In Pennington and Leffell's review of the book by Darrell S. Rigel, the photomicrograph, which does not appear in the book being reviewed, does not show skin tissue with melanoma, as stated in the legend. A photomicrograph showing skin tissue with melanoma appears below. We regret the error.

Photomicrograph of Skin Tissue Showing Melanoma.

Courtesy of Darrell S. Rigel.



N Engl J Med 2005;353:2728-a

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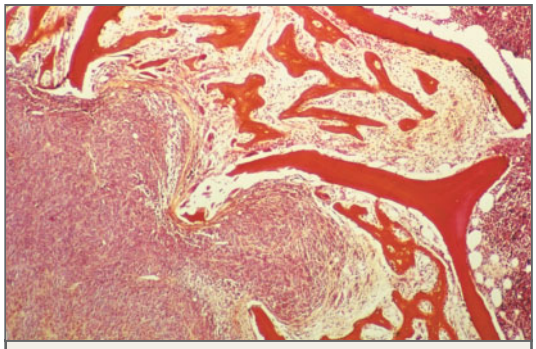

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growth of the congress is entirely due to the success of transplantation. The burgeoning population of kidney recipients has resulted in the growth in the number of transplantation physicians caring for a group whose problems are largely medical.

Medical Management of Kidney Transplantation is a timely, authoritative, multiauthored textbook that will serve the growing population of medical and allied health professionals, as well as those in the pharmaceutical industry who support transplantation. The care of the kidney-graft recipient parallels the care of other solid-organ recipients and has relevance to physicians caring for recipients of other organs.

Other textbooks, regularly updated, have served a similar purpose. However, they include details on organ donation and surgical aspects of kidney transplantation as well as on medical and immunologic aspects. Weir's book, as the title suggests, focuses on medical issues that require considerable depth and breadth of discussion while retaining an awareness of surgical care and complications. This is the strength of the book. The editor's intention was to offer a timely review of the available medical literature and to provide insightful interpretations that would improve medical care. To all this, I would add the need to identify areas of uncertainty and to highlight areas where more research is required.

How well has this intention been accomplished? As expected, there is considerable variation in style and depth from chapter to chapter. The University of Maryland, Baltimore, has one of the largest kidney-transplantation programs in the country, and Weir invited many of his colleagues to contribute to the book. Nonetheless, other North American experts contributed key chapters. The balance is heavily weighted toward clinical rather than basic science. Even the chapter on immune tolerance is geared toward the future of clinical practice. All the chapters are easy to read, well written, and well referenced. For the most part, the recommendations are generic, rather than proscriptive. Many chapters are excellent, notably those covering hematologic complications and liver disease. Several, such as those discussing urologic complications, pregnancy, pathology, imaging, and drug interactions, are remarkably succinct but comprehensive. A few chapters, in which the authors exercise their license to express opinion, border on single-mindedness. Nonetheless, these comments are both valuable and insightful, and although there are topics that overlap in several chapters, repetition is an issue only if one is reading the book cover to cover. Although some topics are treated lightly, such as therapeutic drug monitoring, assessment of the quality of organs from deceased donors, and allocation strategies, the book is comprehensive and has achieved its purpose.

This excellent textbook is now the standard with which all other textbooks on kidney transplantation can be compared. Since transplantation medicine is an evolving art, the book will help all those on the path to improving the quality of life of patients undergoing kidney transplantation.

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NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal's *Web site (www.nejm.org/meetings). The listings can be viewed in their entirety or searched by location, month, or key word.*

TRANSPLANT IMMUNOSUPPRESSION 2005: IMPROVING RECIPIENT OUTCOME

The congress will be held in Minneapolis, Sept. 28–Oct. 1. Deadline for submission of papers is June 30.

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OCCUPATIONAL SAFETY AND HEALTH EDUCATION AND RESEARCH CENTER

The following courses will be offered in Chapel Hill, N.C., unless otherwise indicated: "Certified Hazardous Material Manager (CHMM) Review" (Exam, July 15); "Occupational Health Nursing Certification Review" (July 31–Aug. 2); "28th Annual Occupational Safety and Health Summer Institute" (Marco Island, Fla., July 31–Aug. 4); "Supervising Lead Abatement Programs" (Aug. 18); "Supervising Asbestos Abatement Projects" (Refresher Course, Sept. 1); "Comprehensive Industrial Hygiene (CIH) Review Course" (Sept. 12–16); "Asbestos Operations and Maintenance" (Sept. 26 and 27; Refresher Course, July 11); "Building Inspection and Management Planning for Asbestos" (Oct. 31–Nov. 4; Refresher Course, Sept. 2); and "Certified Safety Professional (CSP) Review Course" (Nov. 14–18).

Contact Occupational Safety and Health Education and Research Center, University of North Carolina, 3300 Hwy. 54 West, Chapel Hill, NC 27516-8264; or call (888) 235-3320 (national) or (919) 962-2101 (North Carolina); or fax (919) 966-7579; or e-mail oshercww@sph.unc.edu; or see http://www.sph.unc.edu/osherc/.

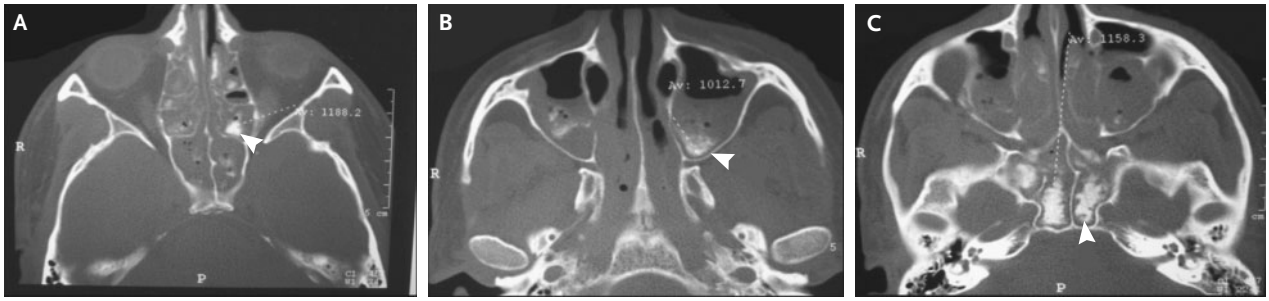
HARRINGTON SPINE SYMPOSIUM

The symposium will be held in Kansas City, Kans., July 28–30.

Contact Dr. Marc Asher, 3901 Rainbow Blvd., MS 3017, Kansas City, KS 66160; or call (913) 588-6174; or fax (913) 588-8796; or see http://www.harringtonsymposium.com.

IMAGES IN CLINICAL MEDICINE

Tsunami Sinusitis



A 35-year-old man was brought to the hospital after sustaining injuries associated with the tsunami in Southeast Asia on December 26, 2004. The patient had inhaled seawater when he nearly drowned. In addition, he had sustained multiple injuries, including a scalp laceration and torn right anterior cruciate and medial collateral ligaments. He had sinus discomfort but no difficulty breathing. Computed tomographic scanning showed fluid and opaque material in the ethmoid (Panel A, arrowhead), maxillary (Panel B, arrowhead), and sphenoid sinuses (Panel C, arrowhead). (For comparison, normally aerated sinuses from another patient can be seen in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) The patient underwent bilateral antral washout, during which green-colored purulent material and sand were removed. Culture of material obtained from the maxillary sinuses showed *Aeromonas veronii*, *Klebsiella pneumoniae*, and *Escherichia coli* on the right side and *E. coli*, *A. hydrophila*, and *Proteus mirabilis* on the left side. The patient received antimicrobial therapy and repair of his right knee ligaments and made a full recovery.

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