The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JULY 28, 2005

Bar Coding for Patient Safety

Alexi A. Wright, M.D., and Ingrid T. Katz, M.D., M.H.S.

A small revolution in patient safety is taking place in the basement of our hospital. Deep underground, in a windowless room about the size of a closet, sits a 6-ft-long hydraulic machine straight out of Willy Wonka's chocolate factory. With the flip of a switch, it spins to life, spitting out drugs on a miniature conveyer belt. Single pills, prepackaged in foil, and bottles intermingle along the track, inching toward the end, where they are each individually bar-coded. The machine is a central part of a new hospital-wide system that is so complex it requires a multimillion-dollar budget to institute yet so simple that grocery stores have been using it for decades to sell bubble gum. Bar coding is the latest technology designed to improve patient safety at a time when hospitals are under increased scrutiny for medical errors.

Any intern can attest to the importance of safeguards in patient care. Two years ago, when we started our internal-medicine residency at Brigham and Women's Hospital in Boston, we were paged dozens of times by diligent pharmacists, gently reminding us to lower the dose of an antibiotic or suggesting alternative medications with better side-effect profiles. Nurses alerted us when they discovered undocumented allergies or had questions about the doses of medications we had prescribed. Our experience was not unique. Every year, hospitals around the country prepare for a new group of interns, imagining an onslaught of errors, but studies show that health care workers make mistakes at every level. This was first brought to the public's attention in 2000, when the Institute of Medicine published the now-famous report *To Err Is Human*. The report documented the incidence of medical mistakes, including data from an early study that showed that 3.7 percent of patients hospitalized in New York State were injured by medical treatments and the finding that nearly 180,000 patients in the United States died each year because of iatrogenic injuries.[1]

One of the most compelling parts of the report concerned data collected by researchers who sought to determine where medical errors occurred and how to stop them, focusing on the biggest culprit — drugs. In an ambitious and expensive study,[2] the researchers prospectively followed thousands of patients admitted to Brigham and Women's Hospital and Massachusetts General Hospital. The study reads like an atlas of medical and human error. For the first time, it was possible to determine exactly when and why adverse drug events occurred. Many were banal — the types of

mistakes people make in the grocery store: writing illegible lists, inadvertently pulling the wrong item off a shelf, or forgetting a critical ingredient. Others were more serious, suggesting that health care workers were operating without enough information about appropriate doses, drug interactions, or particular patients. Physicians made the most mistakes — 39 percent of all adverse drug events were traced to incorrect orders — but half were caught and corrected by nurses or pharmacists. Nurses made almost as many errors (38 percent), but only 2 percent of these mistakes were intercepted, because there were fewer checkpoints between the nurses and the patients.[2]

Public discussions often focus on serious mistakes made by physicians — a sponge left inside a patient after surgery or an inappropriate amputation. Less attention is paid to nursing errors, however. The Harvard study highlights a worrisome fact: most nurses are alone when they administer medication. A number of nursing errors were recently discovered inadvertently when researchers replaced the standard intravenous pumps in the cardiothoracic-surgery intensive care unit with so-called smart pumps designed to prevent mistakes. Smart pumps have built-in danger alerts, clinical calculators, and drug libraries including information on the standardized concentrations of commonly used drugs. The pumps also act as "black boxes" (similar to those found aboard airplanes), recording exactly what is given to the patient and what choices are made. In the study, nurses routinely bypassed danger alerts and drug libraries as much as 25 percent of the time, sometimes administering medications such as propofol, insulin, and heparin at rates 10 times as high as those ordered. As much as 8 percent of the time, nurses gave medications without having a documented order.[3] In the current system (without smart pumps), none of these errors would come to light.

Recently, a few hospitals have started to focus on nursing errors. The Veterans Affairs (VA) hospital system led the way, instituting a national bar-coding program in 1999. The system automated manual labor: each time a physician ordered a medication, the order was immediately transmitted to the pharmacy, where an individual bar code was generated. After verifying the orders, pharmacists sent the labeled medications to the floor, where nurses could compare bar codes embedded in patient identification bracelets against the labels on the medications with grocery-store–type scanners. The program was an overwhelming success: shortly after instituting the system, one VA hospital documented a 24 percent decrease in the rate of medication-administration errors.

Despite this success, only 5 percent of U.S. hospitals currently use bar coding. The Partners HealthCare system, which includes Massachusetts General Hospital and Brigham and Women's Hospital, is one of the most recent health care groups to begin bar coding. Partners administrators have been considering it for more than a decade, but they recognized early on that introducing bar coding would be a herculean endeavor. The system has cost Partners $10 million in start-up expenses and approximately $1 million annually to maintain.

One of the organization's biggest concerns is the potential for losing nurses: by tethering nurses to their portable laptops and scanners, much the same way as patients are attached to their IV poles, we risk disrupting nursing work-flow patterns. Similarly, making nurses accountable for when, where, and how they administer each medication may limit nursing autonomy. This is why Partners is investing half of its multimillion-dollar budget in training to make sure that bar coding, and the electronic system of checks and balances that accompanies it, is well received. The hospitals are paying nurses to attend training sessions and hiring a fleet of "superusers" — nurses on the staff who are computer-literate and specially trained to provide round-the-clock assistance for anyone who needs help (from learning how to use a mouse to planning dosing schedules for the

day). Each nurse now has a wireless laptop computer, a battery-operated scanner, and a cart on which to wheel the space-age technology around. Although many nurses expressed trepidation before using the system, most are now relieved, recognizing that they are catching new errors for the first time.

Several of the nurses we interviewed, however, expressed concern that the new system is too slow to respond in clinical emergencies. Although most of the patient care areas are stocked with common drugs, occasionally a critical medication is not available immediately, and it can take up to an hour to get it from the pharmacy. We have experienced a few such delays, including delays in obtaining antibiotics to treat sepsis, insulin drips for patients with diabetic ketoacidosis, and intravenous diltiazem to slow atrial fibrillation with rapid ventricular response. Fortunately, these are rare occurrences, and the system is suspended in "code" situations when medications are needed instantly.

Early data from the hospital pharmacy suggest that the system is already making a difference in patient safety. Bar coding has reduced drug errors by more than 50 percent, preventing approximately 20 adverse drug events per day.[4] Although the ultimate goal is to protect patients, these measures also save on the bottom line, since the average adverse event costs an estimated $4,700 in extra hospital days and ancillary services — excluding the cost of litigation.[5] When all the kinks have been worked out, perhaps more hospitals can join the increasing number of institutions that have embraced this technology — and can implement patient-safety mechanisms that are long overdue.

Drs. Wright and Katz are residents in internal medicine at Brigham and Women's Hospital, Boston.

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Straight from the Shoulder

John Halamka, M.D.

When I was a resident in emergency medicine, I spent many hours uncovering the identities of John Doe and Jane Doe patients who were unconscious, disoriented, or mute. I searched their belongings for receipts that included an address or scanned their clothing labels for a clue. Sometimes this worked. Often, hours or days passed before a family member was found who knew the patient's medical history and health care preferences. By that time, substantial worry had been endured, and often possibly unwanted medical interventions had occurred.

Today, I lead the information-technology efforts at an academic health center, and I have recently encountered an innovative use of technology that could minimize such difficulties. The Food and Drug Administration has approved an implantable device that can store the medical identifier of a patient. Last December, one of these chips was placed in my right upper arm. Implantation was virtually painless — a few milliliters of local anesthesia and the insertion of a device about as large as a grain of rice (see photograph). It sits in the posterior aspect of my right arm, between the elbow and the shoulder. The days after the implantation were uneventful: no pain, no infection, and no restriction of activities. Now, when a scanner is passed within 6 in. (15 cm) of my arm, my medical identifier is displayed on the screen of a radiofrequency-identification (RFID) reader, and any authorized health care worker can turn to a secure Web site hosted by the manufacturer and retrieve information about my identity and the name of my primary care physician, who can then provide details of my medical history.

The chip consists of several small components enclosed in an unbreakable glass capsule that is partially surrounded by a coating that encourages body cells to adhere to the capsule and prevent it from moving. Although the device relies on the same technology that is used for implanted identification in animals, the frequen-

CORRECTION

Bar Coding for Patient Safety

Bar Coding for Patient Safety . On page 331, in the middle column, lines 11 through 15 should have read, ``Bar coding has reduced drug errors by more than 50 percent, preventing approximately 20 dispensing errors per day that had the potential to harm patients,´´ rather than ``. . . preventing approximately 20 adverse drug events per day,´´ as printed.

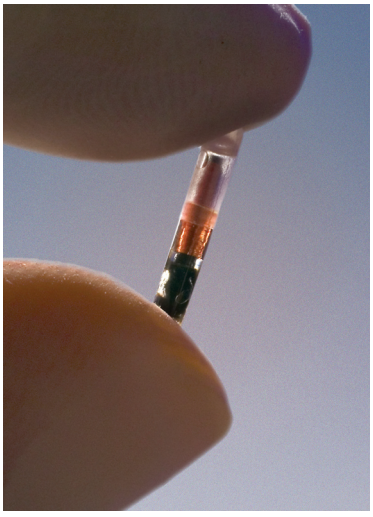
N Engl J Med 2005;353:1640-b

cies used and the manufacturing standards are different. On the basis of experience with pets, the chips can be expected to last at least 10 years and probably much longer than the average human life span. They can safely undergo magnetic resonance imaging (MRI). The device does not generate harmful heat and will not be pulled from my body by an MRI magnet, nor will the magnetic field deactivate the chip. I have flown to several cities since the implantation and have not triggered airline security systems.

A handheld RFID reader scans the chip, which transmits to the reader my medical identifier, a 16-digit number. The chip does not contain demographic or medical data about me. No battery needs replacing. The chip is not an active RFID tag or global-positioning device transmitting information about my location. My identifier was set during the manufacturing process, and it cannot be altered externally.

The primary concern aroused by such technology is that of privacy. Some radiofrequency chips, such as those used at gasoline stations or in automobile-ignition keys, contain encrypted information about a user's account number or information needed to start the car. Chips approved for implantation in humans are not encrypted and thus can be read by many radiofrequency readers.

Since my chip contains only my medical identifier, unauthorized reading would not disclose health information. But nothing is simple. In the film *Minority Report*, Tom Cruise's character strolls by billboards at a shopping mall that change as he approaches in order to deliver customized advertising. Without any interest in who I am, a scanner in a mall could record my presence when I make a purchase and, on a later visit, display a personalized message on a large screen — "Hi, there! You were here three months



ago and purchased a fountain pen. We're having a special on ink today; would you prefer blue or black?" Such "spam," generated by my chip, is a theoretical but possible violator of privacy. Today, no legislation would preclude the scanning of people for anonymous tracking, an activity analogous to what virus-like programs such as "spyware" and "adware" do when they infect our computers after we surf Internet sites. Such a concern is certainly real.

Although future chips may contain cryptographic identifiers that prevent their disclosure to unauthorized readers, hackers are already at work bypassing chip security. This past January, industry experts announced that they had broken the encryption of the Mobil Speedpass and automobile-key security.[1] Using an ordinary personal computer, they "bought" gasoline and started a car without needing the actual chip. Clearly, the technology will improve, but so will the ingenuity of hackers.

Currently, my identifier is listed as one of my medical-record numbers in the computer system of Beth Israel Deaconess Medical Center, which has internal security controls. When a credentialed clinician enters the information read from my chip into the system and retrieves my medical history, that lookup is audited. Inappropriate peeks — which can be monitored by the patient as well as by our privacy officer — result in firing.

For some, implanted health care identifiers might quickly prove useful. For patients with Alzheimer's disease who wander away from home, an identifier that enables caregivers to identify nonverbal or confused patients and determine their health care preferences could be very desirable. However, inserting a chip into a patient who is incapable of giving consent raises ethical issues. Presumably, the patient would have to consent at an early stage of such a disease.

A few emergency departments now have RFID readers that can scan these chips. Since currently very few people (all of them healthy volunteers) have such chips implanted, it is too early to assume that the average caregiver's office will be capable of retrieving patients' information. The technology is not cheap: although the cost of implantation will vary from practice to practice, each chip costs $200 and a reader costs $650. But I believe that patients and their caregivers should discuss the risks and benefits of implanted tags in order to make an informed decision about their appropriateness.

After months of living with the device, I have had no side effects,

no pain, no change in muscle function, and no migration of the chip. I have exposed myself to extremes of temperature, wind, water, and several physical impacts while rock and ice climbing; the chip is working fine. If I want to "upgrade" my chip — replace it with a future version that uses more advanced and detailed industry standards or enhancements — removing it will require only minor surgery.

As I researched implantable identifiers, I found substantial controversy about the notion of being "chipped." A Google search for "RFID implant" yields thousands of pages about Big Brother and *1984* as well as *The X-Files* and the idea of alien abduction. It is clear that there are philosophical consequences to having a lifelong implanted identifier. Friends and associates have commented that I am now "marked" and have lost my anonymity. Several colleagues find the notion of a device implanted under the skin to be dehumanizing. I have not investigated these or other moral, religious, or political implications of having an implanted identifier. I was chipped in order to evaluate the technologic, privacy-related, and medical issues as they affect the provision of patient care. On the basis of my unscientific study with a sample of one, I conclude that there may be appropriate uses, that there are privacy implications that must be accepted by the implantee, and that we need to establish standards that permit seamless, secure access to information.

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Making Antimalarial Agents Available in Africa

Kenneth J. Arrow, Ph.D., Hellen Gelband, M.H.S., and Dean T. Jamison, Ph.D.

An infant in rural Africa has fever. Acetaminophen does not work. The fever spikes, and the father makes his way to the local kiosk and buys malaria medicine — chloroquine — that seems to help but then fails. A day later, the baby is dead.

The outcome has little to do with the curability of the disease and everything to do with economics — the economics of poverty and the economics of antimalarial drugs. It was this aspect of the malaria crisis that the U.S. Agency for International Development asked the Institute of Medicine to examine in 2001.[1]

The Africa Malaria Report 2003 prepared by UNICEF[2] paints a grim portrait of the continent that bears most of malaria's burden at the beginning of the 21st century. Despite "intensified efforts to control the disease," the report states, "the number of children dying of malaria rose substantially in eastern and southern Africa during the first half of the past decade. . . . In West Africa . . . there was little change." No country in sub-Saharan Africa had a "substantial decline" in the disease. The culprit: the slow but imperturbable advance of chloroquine-resistant malaria across Africa. After decades of silently saving millions of lives, chloroquine — inexpensive, safe, and effective — is becoming impotent. One new class of antimalarial drugs, the artemisinins, could take its place.

The artemisinins are widely used in Asia, where resistance to chloroquine first emerged in the 1960s. After Chinese government scientists confirmed the antimalarial properties of compounds extracted from *Artemisia annua* (a plant known for centuries for its medicinal properties), companies in China and Vietnam began producing artemisinin-based drugs. But the African market did not develop, even when chloroquine's days were indisputably numbered.

A major barrier was cost. At their cheapest, artemisinins cost at least 10 times as much as chloroquine. Cost was not the only factor, though. No global alarm had been sounded about the looming crisis because until the creation of the fledgling Roll Back Malaria Partnership at the end of the 1990s, the malaria-control community consisted of a cadre of scattered technical experts. Few heard the warnings of lone voices. In addition, the acknowledged failure of the market to produce drugs for "neglected" diseases meant that there was no trodden path for bringing the Asian production of artemisinins into the international drug arena. (That dynamic has since changed somewhat, with the creation of the Medicines for Malaria Venture, a partnership of public and private agencies for the development of new antimalarial drugs.)

To add to the complexity of the situation, by the late 1990s, the leading authorities on malaria had endorsed the concept of combination therapy as the new standard. The prime motivation was to preserve the effectiveness of the artemisinins and other still-effective antimalarial partner drugs in artemisinin-based combination therapies. As in the treatment of AIDS and tuberculosis, two effective drugs with different mechanisms of action can protect each other from the survival of resistant pathogens. Malaria knows no political boundaries, so for combination therapy to delay the emergence of resistance, it must be used in preference to artemisinin monotherapy as widely as possible. If monotherapies persist in some places, resistant strains will develop and spread globally.

The realities of how malaria is recognized and treated must be considered in the facilitation of widespread access to artemisinin-based combination therapies. There is general agreement (though little hard evidence) that in Africa, the majority of malaria treatments are purchased directly by patients or their surrogates and are used without input from the health care system. Improvement in the overall functioning of health care systems is an obvious long-term goal, but we cannot wait until such systems exist to supply artemisinin-based combination therapies while more and more children die of malaria. Either such therapies must be made available at an affordable price, through the same system that distributes chloroquine, or most people will not get effective treatment for malaria.

One artemisinin-based combination therapy, artemether–lumefantrine (Coartem, Novartis), is currently being produced and has a wholesale price of $2.40 per adult course (reportedly with little or no profit margin), as compared with 10 cents retail for chloroquine. Other formulations should enter the market soon,

Artemisia annua.

with an expected decline in price to less than $1 for an adult course. At the lower level, the global cost of the drugs in artemisinin-based combination therapies would be on the order of $500 million per year — barely noticeable in the budget of any major developed country. Nevertheless, this is an unmanageable cost for countries with per capita incomes of $2,000 per year or less. Subsidies are needed, but how can they best be applied?

There are few options. President George W. Bush, in his statement of June 30, has now made the treatment of malaria an official commitment of the United States. But if the U.S. initiative and others like it operate on a country-by-country basis instead of identifying a mechanism that would permit global subsidies and the global distribution of drugs, they will miss the opportunity to optimize both distribution and the useful lifespan of combination therapies.

It is hard to conceive that subsidizing artemisinin-based combination therapies at a local level — say, through vouchers — would be compatible with the current market-driven distribution system. It is not realistic to invent a new distribution system for antimalarial drugs, particularly when the existing one works reasonably well under the circumstances.

The solution is to allow subsidies to enter at a high international level — at the top of the distribution chain. This requires that the producers of artemisinin-based combination therapies sell directly to some international agency. Then the agency, in turn, can resell to distributors — governments and private wholesalers — at very low prices, the difference being the subsidy. The drugs would then flow down to the end users through the same pathways as chloroquine now does, with the requisite profit margins being taken where the private sector now operates. If these drugs start at a very low price when they enter the supply chain and if their supply is adequate, the price to consumers should be about the same as the current price of chloroquine. This is the heart of the recommendation of the Institute of Medicine.[1]

Centralized procurement from producers will have some important additional advantages. First, it will make it easier to enforce quality standards. Second, the procurement facility will guarantee the purchase of qualifying products for several years without waiting for orders from individual countries, providing an incentive for the drug manufacturers and the farmers who grow *A. annua* to enter the market. Currently, there is an artemisinin shortage. In this case, the long-run commitment is the

solution to the short-term problem. Third, the proposed mechanism for the delivery of foreign aid — as a subsidy through the existing antimalarial-supply chains — is relatively undemanding of institutional capacity on the part of governments. In many of the poorest countries, the scarcest resource is not funding but, rather, the administrative capacity for procurement, financial management, and delivery logistics. This mechanism would bypass those potential bottlenecks.

As simple as the Institute of Medicine's concept appears to be, it requires management of a type that acts. The great need is fortitude on the part of leading development-aid organizations; they have to depart from standard operating procedures. The Institute of Medicine's recommendation has gained some currency as a centerpiece in the highest levels of discussions about the financing of malaria treatment (with more meetings planned), but no commitments have been made to adopt it.

The need for the general use of artemisinin-based combination therapies is by now universally accepted. The international community must recognize the need to finance and organize this use, through relatively uncomplicated steps and relatively modest expenditures.

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

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Making Antimalarial Agents Available in the United States

Alan Magill, M.D., and Claire Panosian, M.D.

"Shooting pains in my head were just one hint that my antimalarial medication couldn't stand up to the mosquitoes of Sierra Leone. The pains weren't bad at first, just faraway flashes like heat lightning. There were other signs, such as dizziness, but I thought I was just reacting to the stifling humidity. The muscle spasms in my right calf must be lack of exercise. I'd been in Freetown a month. After a 9-year civil war, the capital city of the West African country barely has electricity, much less Pilates. It does however have a malaria rate among the highest in the world."[1]

Tales of malaria abound among travelers to Africa, and this account is typical. Someone who is far away from reliable health care is suddenly flattened by heat and a raging headache. Even after receiving antimalarial prophylaxis, the visitor may envision his or her bloodstream swarming with the parasite that causes 9 percent of all deaths in Africa. Without laboratory tests, there is no way to be certain of the diagnosis. The next step for some travelers, including the op-ed writer quoted above, is to locate a pharmacy, buy a blister pack of artemisinin-type tablets (artesunate or artemether–lumefantrine, typically), and take the drugs over the course of several days.

As *Plasmodium falciparum* becomes increasingly resistant to first-line agents such as chloroquine and sulfadoxine–pyrimethamine, artemisinin pills and rectal suppositories (ideally taken in combination with a second antimalarial drug) are the best presumptive treatment in areas in which the organism is highly endemic. The empirical algorithm may not appeal to medical purists, but for travelers it beats the worst-case alternative — death or at least hospitalization with malaria that is severe or complicated, typically with cerebral involvement. For hospitalized patients with life-threatening malaria in Africa and most other areas where falciparum is endemic, the drug of choice is either intravenous quinine or intravenous artesunate.

Now consider another scenario. A traveler or a U.S. soldier recently returned from Africa has fever, chills, and a raging headache and goes to an emergency room in the United States. A blood smear shows anemia, thrombocytopenia, and multiple, intraerythrocytic rings of *P. falciparum*. Moreover, the patient has labored breathing, acidosis, and an altered mental status — danger signs warranting immediate parenteral treatment. You are the attending physician. Neither intravenous quinine nor oral, rectal, or intravenous artemisinins have been approved by the Food and Drug Administration (FDA) or are available in the United States. How quickly can you lay

your hands on intravenous quinidine gluconate, the single parenteral antimalarial agent that is available in this country?

In many hospitals, the answer is not very quickly. Over the past 10 to 15 years, most cardiologists in North America have stopped using intravenous quinidine as an antiarrhythmic agent. At a university medical center in Los Angeles with approximately 600 beds, for example, the only vials of quinidine gluconate purchased during the past five years were replacements for older, expired vials. Other hospitals no longer stock this preparation at all. The drug's manufacturer, Eli Lilly, has continued to maintain supplies despite the lack of a commercial market and ships the drug rapidly whenever a patient at a U.S. health care facility needs intravenous antimalarial treatment. Nonetheless, as quinidine gluconate slowly disappears from hospital formularies, there have been published[2] and anecdotal reports describing adverse patient outcomes attributable to its limited availability.

It is important to note that the side effects of intravenous quinidine — QT-segment prolongation, hypotension, and hypoglycemia, in particular — also restrict its use to hospitalized patients in cardiac-monitored beds. Although it is potentially lifesaving in a critically ill patient with malaria, the drug can also complicate an already precarious situation unless the patient is closely monitored. An antimalarial drug that did not require cardiac monitoring for safe use would be of great benefit, especially to U.S. military forces deployed overseas.

Almost 15 years have passed since the Centers for Disease Control (CDC) stopped disbursing parenteral quinine under an investigational-new-drug (IND) application. Patients with a suspected or confirmed case of severe malaria need immediate antimalarial drug treatment, and the CDC found it difficult to ensure the prompt availability of intravenous quinine under the IND application; switching to intravenous quinidine made sense in 1991 because the agent was much more widely available in hospitals for the treatment of cardiac dysrhythmias. Further development of intravenous artesunate is uncertain as the Walter Reed Army Institute of Research seeks a commercial codevelopment partner. The institute's formulation, produced according to current good-manufacturing practices, began phase 1 clinical trials under U.S. IND status in May of this year. If and when a pharmaceutical company joins the Walter Reed effort, another 24 to 48 months might easily pass before an approved product becomes available for use in U.S. civilian and military patients.

The question is, can we wait that long? Malaria currently causes up to 500 million febrile illnesses and approximately 1 million deaths each year. If new global strategies do not allow oral artemisinin-based combination treatments to flow quickly to communities in Africa and elsewhere where malaria is endemic,[3] some experts predict that the death toll from drug-resistant *P. falciparum* will double in the next 10 years. Supplying artemisinin-based combinations in these settings is a necessity. Over the next decade, however, infections acquired by U.S. citizens traveling abroad, expatriate workers, and overseas military personnel could also climb. On the basis of infection rates recorded in Somalia in 1993[4] and Liberia in 2003, we know that U.S. troops sent to Africa as peacekeepers are highly vulnerable to malaria. FDA-approved and currently available oral drugs such as quinine, mefloquine, and atovaquone–proguanil (Malarone), sometimes paired with adjunct antibiotics, will successfully treat some infected persons in the future, but we know from experience that parenteral treatments will make the difference between life and death for others.

Today, scientists interested in the development of antimalarial drugs are most focused on new drug treatments for the developing world, and understandably so. On the other hand, there is little support from major funding sources for the identification of better preventive medications that would facilitate compliance by civilians and military personnel who are at risk for malaria infection — this despite the fact that most of the roughly 1400 malaria cases reported to the CDC annually, half of which are due to *P. falciparum*, could have been foiled outright with appropriate chemoprophylaxis. If travelers do not use prophylactic medications correctly and subsequently become severely ill with falciparum infection, a safety net of easy, effective parenteral treatment is required. Such patients can surface any time, anywhere.

The economics of developing new drugs for severe malaria in the United States do not make sense for the major pharmaceutical companies that have the expertise to do the job. If such companies are unwilling to develop intravenous artesunate or intravenous quinine because of market realities, then appropriate incentives (such as those outlined in

the current "BioShield" legislation that is meant to foster the development of new products to counteract biologic and chemical terrorism) should be offered to induce them to participate. Alternatively, perhaps it is time to consider the formation of a government-sponsored company that would manufacture these orphan drugs and shepherd their applications through the FDA.

No one wants to lose a patient to falciparum malaria. In 2005, there are simply too many proven and promising tools available for the prevention and treatment of this ancient foe. Happily, June was a month of renewed resolve in terms of the global attack. On June 27, 2005, the Bill and Melinda Gates Foundation, which had already donated $150 million toward the development of a malaria vaccine, announced a new round of global health grants totaling $437 million, roughly 20 percent of which was earmarked for innovative malaria research. On June 30, President George W. Bush pledged more than $1.2 billion over five years to fight malaria in Africa by expanding access to mosquito nets treated with long-lasting insecticides and to indoor spraying, as well as by distributing new, effective drug regimens — primarily artemisinin-based combination therapies — through public- and private-sector outlets in target countries. To be launched in 2006 with an initial $30 million outlay for programs in Tanzania, Uganda, and Angola, the U.S. government investment could eventually reach more than 175 million people in 15 or more African nations.

Coming one week before the Group of Eight summit in Gleneagles, Scotland, the timing of the White House announcement was hardly accidental. Statements released earlier in June by G8 finance ministers underscored the commitment this year to tackling diseases that undermine growth and worsen poverty. With its $12 billion annual price tag in economic loss for Africa, malaria certainly qualifies. The Bush initiative aims to inspire other G8 countries and private foundations to contribute to a multifaceted campaign that could halve malaria deaths within five years among Africa's poorest and most vulnerable citizens.

This is all very good news, except for one ironic fact. Although tens of millions of dollars are now destined to bring much-needed artemisinin-based combination treatments to malaria-plagued residents of Africa, the U.S. government still has no plan to ensure that potentially lifesaving, FDA-approved treatments (intravenous artesunate, intravenous quinine, or oral artemisinins) are available to its own citizens.

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, the U.S. government, or any of the institutions with which the authors are affiliated.

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Studying Herbal Remedies

Wallace Sampson, M.D.

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How plausible are claims that echinacea, or purple coneflower, a perennial that is native to North America, is an effective treatment for viral respiratory disease? Tracing the evolution of views about the benefits of echinacea from the traditions of indigenous populations to modern claims, one finds little rationale for studying the effects of this herbal remedy on colds. Indigenous populations — who used echinacea in various forms, including teas, local applications, and inhaled smoke — had no concept of disease states or their causes, nor could they distinguish medicinal effects from the natural course of an illness. Herbal texts list the use of echinacea by at least 13 tribes of Native Americans for the treatment of such widely diverse conditions as sore mouth and gums, cough, dyspepsia, toothache, bowel complaints, hydrophobia, and snakebite.

The potential for distortion of information about this herb arose between the late 1600s and the

1800s, when native people transmitted information about the uses of herbs to explorers, traders, and healers. Descriptions were translated into French, Spanish, and English and from each of those languages into others. Eventually, 19th-century physicians adopted herbs into their eclectic medicine, along with water cures, homeopathy, and manipulation. Physician H.F.C. Meyer used echinacea in his "blood purifier," a panacea for conditions ranging from migraine to wounds that were difficult to heal. More distortion probably occurred as 19th-century conditions were renamed and reclassified into modern ones.

Emerging as a panacea in 19th-century America, echinacea somehow became popular for the treatment of respiratory illness in Germany. In the early 1900s in the United States, echinacea was used as an "oral anti-infective" and a local application for wound healing; it then fell from favor after the introduction of antibiotics. Modern histories do not connect these trails. The supplement boom that started in the 1960s brought echinacea back to the United States as a cold remedy.

Between 1950 and 1991, more than 200 clinical reports of studies of echinacea appeared. Most of these were of small, inadequately controlled European studies sponsored by industry. Researchers who were looking for confirmation performed scores of in vitro studies on entire specimens of echinacea plants and on parts and extracts of plants. Positive findings included nonspecific stimulation of immune-cell division and cytokine release, but these effects have little or no correlation with clinical results. Nevertheless, advocates claimed that echinacea spurred stimulation of the immune system.

In this issue of the *Journal* (pages 341–348), Turner et al. report a randomized clinical trial of echinacea, now widely advertised as a treatment for viral

respiratory disease. In a study sponsored by the National Center for Complementary and Alternative Medicine (NCCAM), the investigators tested three extracts of the root of the one species, *Echinacea angustifolia*, whose primary constituent group of chemicals had shown some immune-stimulating activity either in vitro or in vivo. The trial was multi-institutional, the numbers of subjects were adequate, and randomization and blinding were accomplished; the investigators used direct nasal viral challenge, a method that has been standardized and used in other trials of treatments for viral respiratory disease. So unless some obscure protocol violation occurred, the trial results are real. The clinical trial found no evidence of any clinically significant efficacy of echinacea.

The search for active fractions usually occurs after a whole substance shows clear efficacy. Investigation of extracts of fractions of echinacea when the results of trials of whole herbs are indeterminate is, at the least, debatable. Previous clinical trials of the whole herb as a treatment for viral respiratory disease had been mixed. Publication bias probably promoted a tendency toward positive reports, and trials that are small and not well controlled tend to show more positive results than do larger trials that are done well. Physicists tell us that negative studies (a sign of nonreproducibility) should carry more weight than positive ones. Manufacturers, whose responsibility it is to prove efficacy to support claims, did not perform definitive larger trials, often claiming a lack of patentability.

The National Institutes of Health (NIH) and pharmaceutical companies have had in place for decades mechanisms to search for potential drugs from natural products. Nevertheless, the NCCAM has developed its own reason for investigating implausible remedies — namely, the popularity of such treatments. It claims to be responding to its mission from the U.S. Congress. But research into implausible remedies rarely produces useful information. Disproof rarely leads the supplement industry to reduce production or the public to decrease use. In fact, advocates often dismiss disproof.[1] The Web page of a naturopathic organization that participated in a recent negative trial of echinacea[2] paraphrased the authors as follows: "Weber and the other researchers conclude that other echinacea preparations and dosing regimens may be effective for the treatment of colds, even though the product they tested in children was not."[3]

Trials of effective treatments with objective end points usually show acceptable, consistent results. But alternative remedies are generally less effective or ineffective, and randomized clinical trials of these remedies measure mostly subjective symptoms. Systematic reviews of these remedies show positive and negative results distributed around the zero-effect line.[4] This finding is accounted for partly by investigators' reliance on smaller studies, partly by publication bias, and partly by inconsistent study criteria, including various entry criteria, various outcome measures, and various population bases. Inconsistent outcomes from studies of alternative treatments seem to be the norm. In addition, despite adequate internal reproducibility, there is no adequate external validation for the various scales used in the evaluation of randomized clinical trials. That means there is a lack of certainty that the results of systematic reviews reflect reality. Nor is there a formula for assessing the relative validity of the conflicting results or a consensus either on how to interpret results of systematic reviews or on the proportion of negative trials necessary to declare a method to be ineffective. Reviewers simply create a consensus estimate. (Neither are there standards for validating reviewers' qualifications, expertise, or opinions.)

Carrying the argument further, there is no "demarcation of the absurd," a point at which it is unwise to pursue an investigation further.[5] Today's literary and editorial correctness often dismisses such a conclusion as evidence of bias. Instead, we find repeated clinical trials, redundant systematic reviews of implausible methods, and indeterminate conclusions.

The inability of randomized clinical trials and systematic reviews to establish inefficacy in research into alternative treatments contributes to a recent loss of bearings. Researchers and advocates of alternative medicine present a mass of information with inadequate heuristics for making sense of it and insufficient standards for making use of it. Should there be studies of other echinacea species, of other parts of the plant, and of each extract of each part of each plant on each cold and each influenza virus? Should these studies be repeated in various combinations, with dose modifications? Why? The possible combinations increase geometrically. Since 1999, the NIH has spent almost $1.5 billion in grants for research into alternative methods. NCCAM has spent almost half that amount and has found no evidence of efficacy and little evidence of inefficacy. NCCAM has three more randomized clinical trials of echinacea that are currently active. As long as research sponsored by NCCAM and private foundations continues, advocates of alternative treatments can claim that a state of equipoise exists when, in fact, the issues should have been settled on the basis of previous knowledge.

It is time for reassessment. First, there is an answer to the question, "Why are we doing randomized clinical trials of folkway uses of herbs and sectarian remedies?" The answer is that proponents and evaluators have excluded plausibility from the equation. What is needed is knowledge-based medicine, with randomized clinical trials of treatments with histories that indicate some reasonable chance of efficacy. This approach mandates a medicine based on evidence that has passed through the sieve of plausibility and that is consistent with basic sciences, other applied sciences, and history — all molded by wisdom and common sense. NCCAM, if it is to justify its existence, must consider halting its search for active remedies through clinical trials of treatments of low plausibility. A wealth of information also awaits discovery in the psychology of personal beliefs in irrational proposals, in the study of erroneous thinking, and in the study of the mechanisms behind errant social–medical trends such as the alternative-medicine movement.

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THIS WEEK *in the* JOURNAL

ORIGINAL ARTICLE

Echinacea for Rhinovirus Infections

Either placebo or a preparation of chemically defined extracts from *Echinacea angustifolia* root was administered to 399 volunteers before or after inoculation with rhinovirus. These rigorously controlled studies found no evidence that echinacea is effective in treating or preventing the common cold.

SEE P. 341; PERSPECTIVE, P. 337; CME, P. 438

ORIGINAL ARTICLE

Perioperative Beta-Blockade and Cardiac Risk

In this large, retrospective cohort study of patients who underwent major noncardiac surgery, perioperative beta-blockade was associated with a significantly reduced risk of death in the hospital among those who were at high risk but not among those at low risk. These data support recommendations for wider use of perioperative beta-blockade in high-risk patients and need to be confirmed in a large randomized trial.

SEE P. 349; EDITORIAL, P. 412; CME, P. 439

BRIEF REPORT

PML in a Patient with Crohn's Disease

In a man with Crohn's disease who was treated with natalizumab and subsequently died, reexamination showed that the fatal lesion was progressive multifocal leukoencephalopathy and not an astrocytoma. Analysis of serial serum specimens showed that JC virus first appeared about three months after the initiation of natalizumab therapy.

SEE P. 362; EDITORIALS, P. 414 AND 417

BRIEF REPORT

PML during Treatment for Multiple Sclerosis

A 46-year-old woman with multiple sclerosis died from progressive multifocal leukoencephalopathy after receiving 37 doses of natalizumab plus interferon beta-1a as part of a clinical trial. At autopsy, there were diffuse macroscopic and microscopic PML lesions. JC virus was identified in cerebrospinal fluid before death and in brain tissue at autopsy. There was extensive necrosis and cavitation, with no inflammatory response.

SEE P. 369; EDITORIALS, P. 414 AND 417

BRIEF REPORT

PML after Natalizumab for Multiple Sclerosis

Progressive multifocal leukoencephalopathy developed in a man with multiple sclerosis while he was receiving interferon beta-1a and natalizumab. Quadriparesis, global aphasia, and minimal responsiveness ensued. Three months after natalizumab was stopped and after receiving cytarabine, he became alert and communicative, though he had continued neurologic disabilities.

SEE P. 375; EDITORIALS, P. 414 AND 417

SPECIAL ARTICLE

Discontinuous Health Insurance Coverage of Children in the United States

With data from the 2000 and 2001 National Health Interview Surveys, the authors estimate that 6.6 percent of children in the United States had been uninsured for the previous 12 months and an additional 7.7 percent had had insurance for only part of the year. Children who had been uninsured for all or part of the year were much more likely to go without needed medical care than were children who had continuous coverage.

SEE P. 382; EDITORIAL, P. 418

CLINICAL PRACTICE

Cervical Radiculopathy

A 37-year-old woman presents with a two-week history of severe neck pain radiating to her left shoulder girdle and extending to the arm, forearm, and dorsum of the hand. Physical examination reveals weakness of her left triceps, finger extensors, and wrist flexors, as well as hypoesthesia of the third digit and a diminished triceps reflex. How should her case be managed?

SEE P. 392; CME, P. 437

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

A Man with a Mass in the Liver

A 57-year-old man with chronic active HBV infection was found to have a mass in the liver on routine screening. The results of a fine-needle aspiration biopsy suggested hepatocellular carcinoma. A multidisciplinary group discusses pathophysiology and management.

SEE P. 401

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2005 VOL. 353 NO. 4

An Evaluation of *Echinacea angustifolia* in Experimental Rhinovirus Infections

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ABSTRACT

BACKGROUND

Echinacea has been widely used as an herbal remedy for the common cold, but efficacy studies have produced conflicting results, and there are a variety of echinacea products on the market with different phytochemical compositions. We evaluated the effect of chemically defined extracts from *Echinacea angustifolia* roots on rhinovirus infection.

METHODS

Three preparations of echinacea, with distinct phytochemical profiles, were produced by extraction from *E. angustifolia* roots with supercritical carbon dioxide, 60 percent ethanol, or 20 percent ethanol. A total of 437 volunteers were randomly assigned to receive either prophylaxis (beginning seven days before the virus challenge) or treatment (beginning at the time of the challenge) either with one of these preparations or with placebo. The results for 399 volunteers who were challenged with rhinovirus type 39 and observed in a sequestered setting for five days were included in the data analysis.

RESULTS

There were no statistically significant effects of the three echinacea extracts on rates of infection or severity of symptoms. Similarly, there were no significant effects of treatment on the volume of nasal secretions, on polymorphonuclear leukocyte or interleukin-8 concentrations in nasal-lavage specimens, or on quantitative-virus titer.

CONCLUSIONS

The results of this study indicate that extracts of *E. angustifolia* root, either alone or in combination, do not have clinically significant effects on infection with a rhinovirus or on the clinical illness that results from it.

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N Engl J Med 2005;353:341-8.

THE COMMON COLD IS A BENIGN AND self-limited illness most commonly caused by the rhinoviruses. Although the importance of the common cold derives primarily from its frequency and from the enormous socioeconomic impact it has, it is clear that the common cold in general and rhinovirus infection in particular are associated with significant medical consequences.[1-8] There are no specific antiviral treatments for rhinovirus infection. Perhaps because of the lack of specific therapies, concern about the risks relative to the benefits of treatments for symptoms, and the relatively benign nature of the common cold, there is wide interest in the use of alternative medicines for the treatment of this illness.

Echinacea angustifolia roots were originally used by North American Indians to treat a variety of infections and wounds. In the late 1800s, these echinacea preparations became popular as remedies for the common cold. There has been renewed interest in echinacea in the United States since the passage of the Dietary Supplement Health and Education Act in 1994 liberalized the regulation of herbal medicines. There are three species of echinacea, with different phytochemical characteristics, that are used for medicinal purposes. The phytochemical composition of echinacea preparations may also vary owing to differences in the part of the plant used, the method used to extract the material in the preparation, and even the geographic location and time of year that the plant is harvested.[9] In spite of the variability among echinacea preparations, only recently have there been attempts to standardize and characterize the material used in clinical studies.

The experimental model for colds caused by rhinoviruses is a well-established, carefully controlled model for the study of the pathogenesis and treatment of the common cold.[10,11] The purpose of our study was to use the experimental model and carefully defined preparations of echinacea to evaluate systematically the effect of different echinacea constituents on rhinovirus infection and common-cold symptoms.

METHODS

VOLUNTEERS

Healthy young adult volunteers were recruited for this study from the University of Virginia community. Volunteers susceptible to rhinovirus type 39, as evidenced by a serum-neutralizing antibody titer of 1:4 or less, were invited to participate. Written informed consent, in a form approved by the Human Investigations Committee of the University of Virginia, was obtained from all volunteers before study participation, and subjects were compensated for participating.

STUDY MEDICATION

The echinacea preparations for the study were developed from a single lot of *E. angustifolia* root. The root material was extracted with either supercritical carbon dioxide, 60 percent ethanol, or 20 percent ethanol to produce three different preparations. The placebo for the study contained a mixture of alcoholic beverages, denatonium benzoate (250 ppm), and tap water. The treatments were given three times each day as a 1.5-ml tincture containing the equivalent of 300 mg of echinacea root. The 437 volunteers were randomly assigned in blocks to receive one of the seven treatment regimens (described below) to ensure that the regimens would be equally distributed over the course of the study. The participants and all study staff at the University of Virginia were blinded to the group assignments until all data had been collected and transmitted to the study statistician.

CONDUCT OF THE STUDY

Six cohorts of volunteers were studied between May 2002 and March 2004. The numbers of subjects in the first five cohorts ranged from 69 to 84; 45 volunteers were enrolled in the sixth cohort. The study was divided into a prophylaxis phase (day −7 until virus challenge on day 0) and a treatment phase (virus challenge to day 5). Within each cohort, there were seven possible treatment assignments, with carbon dioxide extract, 60 percent extract, or 20 percent extract given during both phases or with placebo given during the prophylaxis phase and the carbon dioxide extract, 60 percent extract, or 20 percent extract given during the treatment phase. The control group received placebo throughout both phases of the study period. Volunteers took their assigned study medication as outpatients on days −7 to 0. On day 0, all asymptomatic volunteers were challenged with rhinovirus type 39 and then isolated in individual hotel rooms for the remainder of the study. Between virus challenge and the morning of day 5 of the study, the symptom scores of the subjects were evaluated every morning and evening, and a nasal lavage

was performed each morning after symptom scoring was completed. Approximately three weeks after the virus challenge, all volunteers returned to the study site to have blood collected for testing for antibody to rhinovirus type 39.

ASSESSMENT OF COMPLIANCE

A known volume of study medication was provided during the prophylaxis phase, and compliance was assessed through the measurement of the volume of medication returned. The study staff dispensed and observed the consumption of all medications during the treatment phase.

ASSESSMENT OF BLINDING

The adequacy of the study's blinding procedures was assessed according to the subjects' responses when asked which study medication they believed they were taking ("active," "placebo," or "don't know"). This question was asked at the end of the prophylaxis phase just before virus challenge and again after administration of the third dose of study medication in the treatment phase of the trial.

CHALLENGE VIRUS

The challenge virus used for this study was rhinovirus type 39. This virus has been tested for safety according to consensus guidelines.[12] All of the subjects were inoculated with approximately 100 50 percent tissue-culture infectious doses of virus.

VIRUS ISOLATION AND SEROLOGY

Nasal-lavage specimens collected on day 0 before virus challenge were cultured in HEp-2, rhesus-monkey–kidney, A549, and fibroblast cells for the detection of unsuspected viral infections. Nasal-lavage specimens collected on study days 1 to 5 were cultured for rhinovirus by standard methods, as previously described.[13] Serum specimens were tested for neutralizing antibody to rhinovirus type 39 by a standard microtiter assay.[14] Volunteers in whom rhinovirus type 39 was isolated from at least one postinoculation specimen, in whom serum-neutralizing antibody to rhinovirus type 39 was increased by a factor of four, or both, were considered infected with the study virus. Viral titers in the original nasal-wash specimens were determined from specimens stored at −80°C by culturing serial dilutions, in which virus was serially diluted by a factor of 10, in microtiter plates of MRC-5 cells, as previously described.[13]

ASSESSMENT OF SYMPTOMS

Symptom scores were recorded by members of the study staff. Volunteers were asked to rate their symptoms of sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, malaise, and chilliness on a scale of 0 to 4; the numbers corresponded to a symptom severity of absent, mild, moderate, severe, or very severe. Scoring of symptoms was done before virus challenge and then every morning and evening on study days 1 to 5. Each morning, symptom scores were recorded before the nasal-wash procedure. The daily symptom score for each symptom on study days 1 to 5 was defined as the higher of the two scores reported for the symptom on each day. Volunteers who had a symptom score of at least 6 for the five days after challenge and either at least three days of rhinorrhea or the subjective impression that they had a cold were defined as having a clinical cold. The nasal-secretion weight per 24-hour period was also determined by a previously described method[13] for each volunteer on study days 0 to 5.

ASSESSMENT OF INFLAMMATION

The interleukin-8 concentration was measured in nasal-lavage specimens with the use of a commercially available enzyme-linked immunosorbent assay, as previously described.[15] For determination of the polymorphonuclear leukocyte concentration, an aliquot of nasal-lavage specimen was stained with acridine orange, and then the polymorphonuclear leukocytes, identified by size and nuclear morphology, were counted in a hemacytometer.

PHYTOCHEMICAL ANALYSIS

Phytochemical analysis of the extracts to detect the alkamides was performed with the use of mass spectroscopy. A photometric method was used for the analysis of the polysaccharides.[16] A complete description of the methods used for the phytochemical analysis is provided in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

On the basis of previous data for rhinovirus type 39,[13] it was assumed that placebo-treated subjects would have an infection rate of 85 percent and a mean (±SD) total symptom score of 17.7±13.5. With these assumptions, in a sample size of 50 subjects per active treatment group, with 100 subjects in the placebo group, a 20 percent reduction in the

infection rate or a 35 percent reduction in the total symptom score would be detected, with a two-sided type I error of 0.05 and a power of 80 percent.

The evaluation of efficacy in the experimental model assumed that subjects were equally susceptible to the study virus and that all were infected with the same pathogen. Subjects who were found retrospectively to have acute antibody titers greater than 1:4 or in whom a viral respiratory pathogen was isolated from the nasal-lavage specimen on day 0 were excluded, by protocol, from the data analysis.

The primary end point for the prophylaxis phase of the study (i.e., treatment with echinacea from study day −7 through study day 5) was the comparison of the proportion of volunteers who became infected with rhinovirus in each group with the proportion infected in the placebo group. This was performed as six pairwise comparisons with the use of the chi-square analysis. This analysis was supplemented with a multiple logistic-regression analysis that included as covariates the baseline antibody titer, the baseline interleukin-8 concentration in the nasal-lavage specimen, age, sex, and race. The primary end point for the subjects given echinacea as treatment (i.e., those volunteers treated with echinacea only from virus challenge to study day 5) was the comparison of the total symptom score for the infected subjects in each treatment group with the total symptom score for the infected subjects in the placebo group. This comparison was made by analysis of variance, supplemented with a multiple logistic-regression analysis, as described above.

Planned secondary analyses included evaluation of the different study groups with regard to effects on the incidence of clinical colds, effects on quantitative virus titer in nasal secretions, effects on individual symptoms, and effects on polymorphonuclear leukocytes and interleukin-8 as markers of intranasal inflammation.

All reported P values are two-sided and unadjusted for multiple tests. An interim safety analysis was performed after each cohort was discharged from the study; no interim efficacy analysis was carried out.

RESULTS

PHYTOCHEMICAL ANALYSIS OF EXTRACTS

Analyses revealed that the supercritical carbon dioxide extract contained no polysaccharides but did contain 73.8 percent alkamides; the 60 percent ethanol extract contained 48.9 percent polysaccharides and 2.3 percent alkamides; and the 20 percent ethanol extract contained 42.1 percent polysaccharides and only 0.1 percent alkamides. Assays for caffeic acid derivatives revealed that the 60 percent ethanol extract contained 0.16 mg per milliliter of cynarine; however, echinacoside was not detectable in any extract.[17] Details of the phytochemical results are provided in the Supplementary Appendix. Repeated analyses of the study treatments over the course of the study ensured that the composition of the treatments remained constant.

STUDY SUBJECTS

Four hundred thirty-seven volunteers were randomly assigned to receive study medication (Fig. 1). Eighteen subjects who had undergone randomization were not challenged with study virus because of voluntary withdrawal from the study (8 subjects) or because an illness developed before virus challenge (10 subjects). Of the 419 subjects who were challenged with virus, 2 withdrew from the study before data were collected, and in 18 there was either an antibody titer to the challenge virus of greater than 1:4 in the serum sample collected on day 0 or a viral respiratory pathogen isolated from the nasal-lavage specimen collected before the virus challenge. These 20 volunteers were excluded by the study protocol from the data analysis.

The mean (±SD) age of the 399 subjects was 20.8±3.3 years. Of these, 240 subjects (60 percent) were female; 1 (0.3 percent) was self-classified as American Indian, 37 (9.3 percent) were self-classified as Asian, 42 (11 percent) as black, 316 (79 percent) as white, and 3 (0.8 percent) as being of mixed race. The random assignment of subjects to the treatment groups resulted in a balanced distribution with regard to age and sex, with the exception of the treatment group that received the 60 percent extract, in which women were overrepresented (75 percent, P=0.02) as compared with the placebo group.

COMPLIANCE AND BLINDING

Evaluation of compliance during the prophylaxis phase of the study revealed that more than 90 percent of the subjects took at least 80 percent of their medication. During the treatment phase, there were two missed doses of study medication as a result of doses held because of side effects. Evaluation of blinding revealed that the proportion of volunteers who believed they were taking the active med-

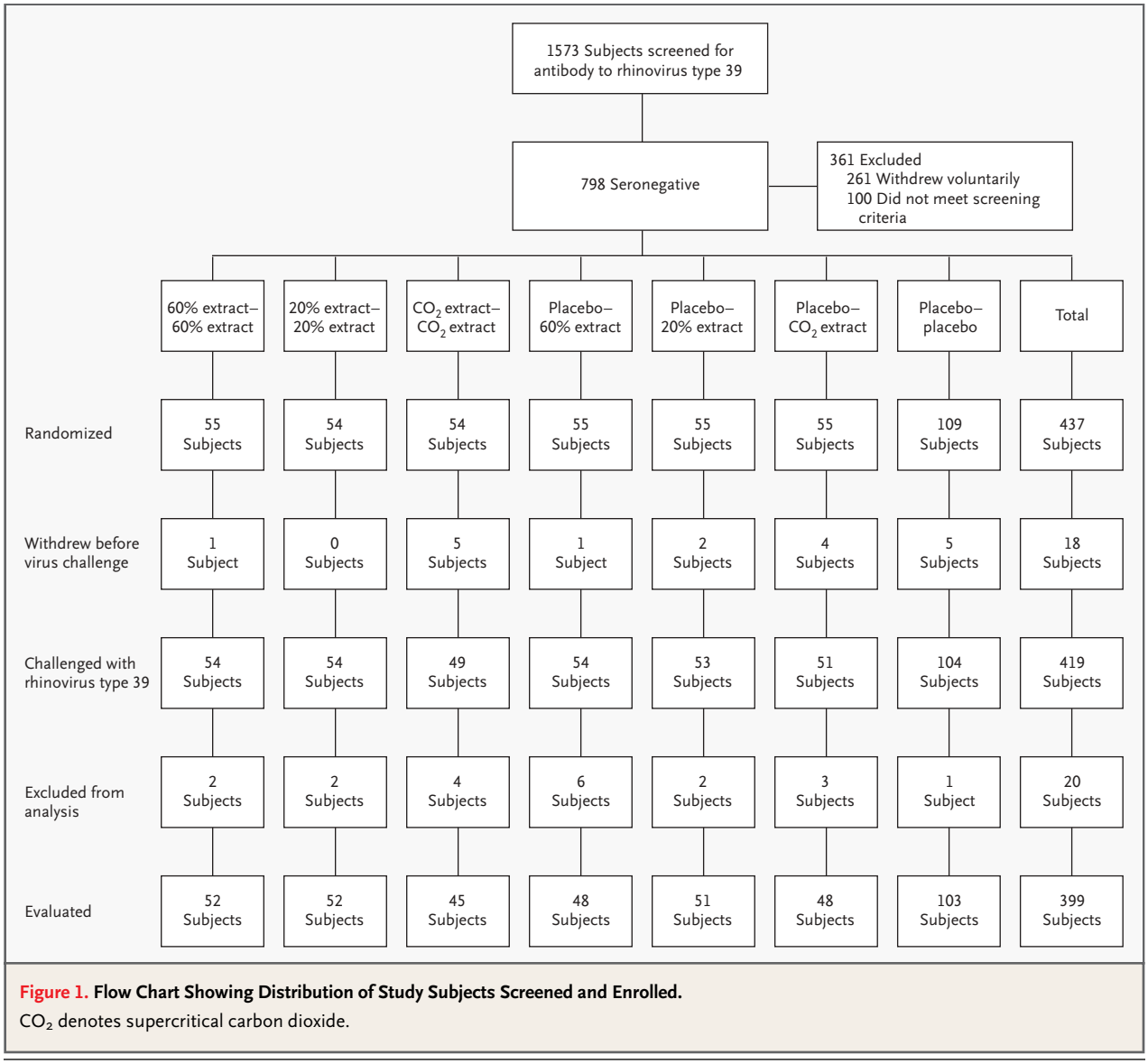

Figure 1. Flow Chart Showing Distribution of Study Subjects Screened and Enrolled.
CO_2 denotes supercritical carbon dioxide.

ication during the treatment phase of the study ranged from 21 of 51 (41 percent) to 24 of 48 (50 percent) in the active-treatment groups; in the placebo group, 37 of 103 volunteers (36 percent) believed they were receiving the active medication ($P=0.63$ according to the chi-square analysis for all groups).

EFFECT OF ECHINACEA ON INFECTION

Prophylaxis with these echinacea preparations had no significant effect on rhinovirus infection (Table 1), and there was no effect on the infection rate in the groups that received echinacea only in the treatment phase of the study. The quantitative virus titer also was not affected by either prophylaxis or treatment with these echinacea preparations.

EFFECT OF ECHINACEA ON SYMPTOMS

Treatment with these echinacea preparations had no significant effect on symptoms associated with rhinovirus, whether assessed by the total symptom score or by the proportion of subjects with clinical colds (Table 1). There was also no effect of either prophylaxis or treatment on the course of the illness (Fig. 2). Evaluation of nasal-secretion weights as an objective measure of severity also revealed no beneficial effect. During the prophylaxis phase, nasal-secretion weights (mean ±SD)

Table 1. Effect of Various Extracts of *E. angustifolia* Root on Rhinovirus Infection and Common-Cold Illnesses.*

Treatment Day –7 to 0	Treatment Day 0 to 5	No. of Subjects	No. Infected (%)†	95% CI for Difference in Infection Rate vs. Placebo‡	P Value for Difference in Infection Rate vs. Placebo	No. of Clinical Colds in Infected Subjects (%)	Mean Total Symptom Score§
CO_2 extract	CO_2 extract	45	40 (89)	–0.07 to 0.15	0.57	25 (62)	15.45±2.34
60% extract	60% extract	52	42 (81)	–0.09 to 0.17	0.46	24 (57)	13.21±1.91
20% extract	20% extract	52	48 (92)	–0.03 to 0.17	0.22	24 (50)	12.06±1.74
Placebo	CO_2 extract	48	43 (90)	–0.06 to 0.16	0.48	27 (63)	14.60±1.70
Placebo	60% extract	48	44 (92)	–0.03 to 0.17	0.28	33 (75)	19.20±2.28
Placebo	20% extract	51	44 (86)	–0.11 to 0.13	0.89	28 (64)	15.64±1.97
Placebo	Placebo	103	88 (85)	Reference group	—	58 (66)	15.05±1.43

* Plus–minus values are means ±SE. CI denotes confidence interval, and CO_2 supercritical carbon dioxide.
† The P value for homogeneity for the infection rates is 0.58.
‡ Negative numbers indicate a higher infection rate for placebo, and positive numbers a higher rate for echinacea treatment.
§ The total mean symptom score is the sum of symptom scores on days 1 to 5. Higher scores indicate more severe symptoms.

were 17.2±22.5 g in the subjects who received carbon dioxide extract, 17.6±19.7 g in those who received 60 percent ethanol extract, and 19.3±29.4 g in those who received 20 percent ethanol extract. The nasal-secretion weights in subjects who received placebo during the prophylaxis phase and carbon dioxide extract, 60 percent extract, and 20 percent extract during the treatment phase were 20.3±23.3 g, 33.1±32.2 g, and 15.5±14.0 g, respectively. The nasal-secretion weight in subjects who were treated with placebo in both study phases was 21.4±27.9 g. A comparison of the severity of individual symptoms revealed no significant effect of the echinacea preparations on any of the symptoms assessed (data not shown).

EFFECT OF ECHINACEA ON INFLAMMATORY MARKERS

The effect of echinacea on rhinovirus-induced inflammation was assessed by measurement of interleukin-8 and polymorphonuclear-leukocyte concentrations in nasal-lavage specimens. Neither prophylaxis nor treatment with the echinacea preparations had a significant effect on either the interleukin-8 response or the polymorphonuclear-leukocyte response to rhinovirus infection. As expected, there was a significant correlation between the interleukin-8 and polymorphonuclear-leukocyte responses and symptom severity.

ADVERSE EVENTS

During the prophylaxis phase of the study, 19 of the 437 randomized subjects reported adverse events. Adverse events judged to be possibly related to the study medication were reported by 4 of 163 (2 percent) of the subjects receiving an echinacea preparation and by 5 of 274 (2 percent) receiving placebo. During the treatment phase of the study, 15 of 315 (5 percent) of the subjects receiving an echinacea preparation reported an adverse event that possibly was related to the treatment, as compared with 4 of 104 (4 percent) of the placebo-treated subjects. Gastrointestinal side effects were the most common events, reported by 12 subjects in the echinacea groups and 4 subjects in the placebo group.

DISCUSSION

The effect of echinacea on common-cold illnesses has been assessed in a number of clinical studies in which various echinacea preparations and study designs were used. Despite the large number of studies, recent systematic reviews have concluded that the effectiveness of echinacea remains unproved.[18-20] One of these reviews specifically cited the need for studies that involve chemically well-defined preparations, clearly defined illnesses, and early intervention.[20] The purpose of our study was to evaluate the effect of root extracts of *E. angustifolia* on rhinovirus infection and illness in a manner that would permit the systematic evaluation of the contribution of different echinacea constituents to any observed treatment effect. The alkamides, polysaccharides, and caffeic acid derivatives present in extracts of echinacea have demonstrated biologic activity both in vitro and in vivo (reviewed in the Sup-

plementary Appendix and in Bauer[9] and Barrett[19]). It has been proposed that these constituents, either alone or in combination, are the active ingredients in commercially available echinacea preparations. The methods used for extraction of the plant material in our study produced extracts with different concentrations of these putative active constituents. None of the extracts had a detectable effect on rhinovirus infection or illness.

Echinacea products available in the United States are made from the roots, the whole plant, or aerial parts of *E. angustifolia*, *E. pallida*, or *E. purpurea*. These products may be formulated as powdered plant material, alcoholic tinctures, tea preparations, or pressed juice of the aerial parts. Variations in species, plant parts, extraction procedures, and manufacturing processes may affect the chemical constituents or ratios of selected constituents in the final preparation.[9] Specific chemical constituents have various biologic effects (see the Supplementary Appendix), but there have been no previous studies that have compared the clinical effects of different echinacea preparations. For this study, we chose to use experimental extracts of *E. angustifolia*, the species originally used by the Native Americans of the American Midwest and recently endorsed by the World Health Organization for treatment of the common cold.[21]

The experimental model for rhinovirus infection was used for this study. Previous experience with this model for the evaluation of conventional antiviral therapies and treatments for symptoms of the common cold has demonstrated that the experimental model accurately predicts the effectiveness of treatments in the natural setting.[22,23] The reduced variability afforded by the model appears to increase the apparent effect size for effective treatments.[24]

The results of this study demonstrate that, as tested, the putative active constituents of *E. angustifolia* do not have clinically significant effects on rhinovirus infection or illness. There are several considerations for the generalizability of the results of our study, which attempted to correlate the phytochemical composition of echinacea extracts with clinical efficacy. The potential sources of variation in different echinacea preparations include plant species, the method of extraction, the part of the plant that is used, and perhaps even the location and season of cultivation. The polysaccharides and alkamides of echinacea have biologic activity and are generally perceived as the active components of these treatments. It is conceivable, however, that other chemical constituents or combinations of constituents that were not tested in this study have important biologic effects. It is also possible, although unlikely, that echinacea is effective for the treatment of respiratory pathogens other than rhinovirus. Given the great variety of echinacea preparations, it will be difficult to provide conclusive evidence that echinacea has no role in the treatment of the common cold. Our study, however, adds to the accumulating evidence that suggests that the bur-

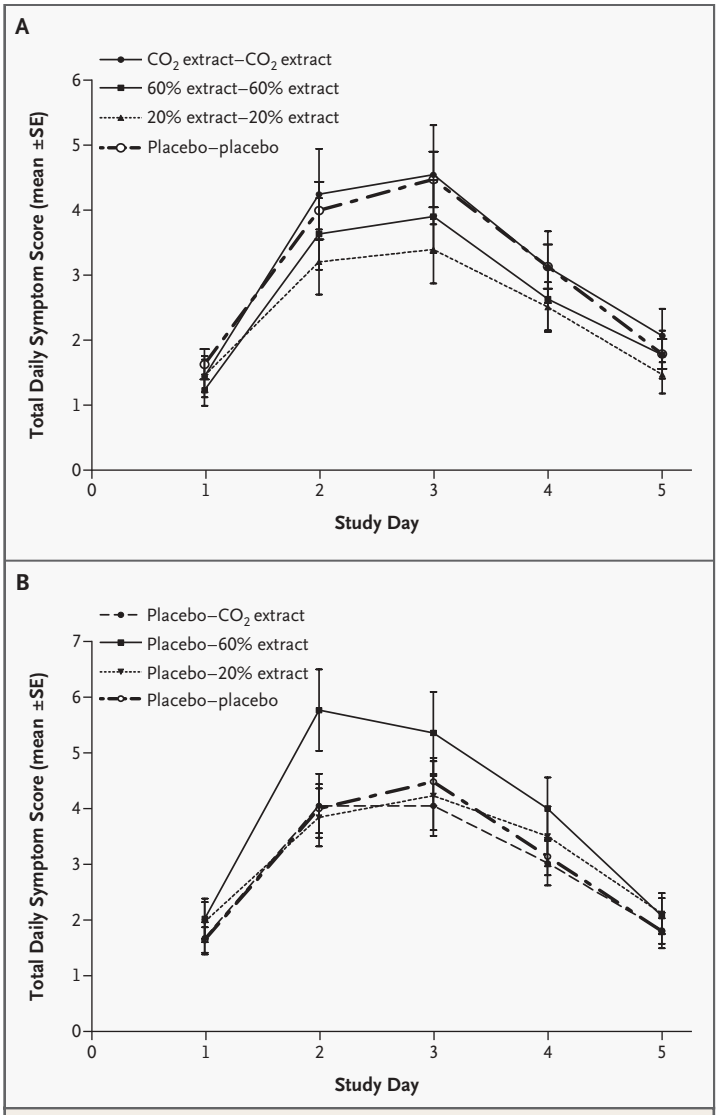

Figure 2. Total Symptom Scores by Study Day in Subjects Who Were Treated with Root Extracts of *E. angustifolia* Either Prophylactically (Panel A) or after Virus Challenge (Panel B).

CO_2 denotes supercritical carbon dioxide.

den of proof should lie with those who advocate this treatment.

Supported by a grant (R01 AT001146) from the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH).

Dr. Turner reports having served as a consultant for Wyeth Consumer Healthcare, Schering-Plough Research Institute, Nordic Phytopharma A/S, the Dial Corporation, and Procter & Gamble and having received grant support from Biopolymer Engineering, the Dial Corporation, and Procter & Gamble. Dr. Gangemi reports having received grant support from the U.S. Department of Defense.

The contents of the article are the sole responsibility of the authors and do not necessarily represent the official views of the NCCAM or the NIH.

We are indebted to Patsy Beasley, R.N., who coordinated the human volunteer portions of the study with assistance from Marilyn Potter, R.N.; and to Dr. Birgit Classen of the Institute of Pharmaceutical Biology, Christian-Albrechts-University, Kiel, Austria, who performed the polysaccharide and glycoprotein analyses.

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ORIGINAL ARTICLE

Perioperative Beta-Blocker Therapy and Mortality after Major Noncardiac Surgery

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ABSTRACT

BACKGROUND

Despite limited evidence from randomized trials, perioperative treatment with beta-blockers is now widely advocated. We assessed the use of perioperative beta-blockers and their association with in-hospital mortality in routine clinical practice.

METHODS

We conducted a retrospective cohort study of patients 18 years of age or older who underwent major noncardiac surgery in 2000 and 2001 at 329 hospitals throughout the United States. We used propensity-score matching to adjust for differences between patients who received perioperative beta-blockers and those who did not receive such therapy and compared in-hospital mortality using multivariable logistic modeling.

RESULTS

Of 782,969 patients, 663,635 (85 percent) had no recorded contraindications to beta-blockers, 122,338 of whom (18 percent) received such treatment during the first two hospital days, including 14 percent of patients with a Revised Cardiac Risk Index (RCRI) score of 0 and 44 percent with a score of 4 or higher. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk; among the 580,665 patients with an RCRI score of 0 or 1, treatment was associated with no benefit and possible harm, whereas among the patients with an RCRI score of 2, 3, or 4 or more, the adjusted odds ratios for death in the hospital were 0.88 (95 percent confidence interval, 0.80 to 0.98), 0.71 (95 percent confidence interval, 0.63 to 0.80), and 0.58 (95 percent confidence interval, 0.50 to 0.67), respectively.

CONCLUSIONS

Perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major noncardiac surgery. Patient safety may be enhanced by increasing the use of beta-blockers in high-risk patients.

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N Engl J Med 2005;353:349-61.

More than 20 million operations are performed annually at hospitals throughout the United States,[1] and although advances in operative and anesthetic techniques have reduced the risks associated with many procedures, some 1 in 10 patients can be expected to have a complication within 30 days after undergoing major surgery.[2] Although they occur infrequently, postoperative cardiovascular complications are associated with a substantial risk of other complications and death,[3,4] and preventing such complications is often the rationale for preoperative medical consultation.

Although the problem of postoperative myocardial infarction has been recognized for over 50 years,[5] few prevention measures have proven effective. Conventional strategies have relied on prediction instruments to identify patients at heightened cardiac risk,[6-9] noninvasive testing, cardiac catheterization followed by revascularization in selected patients, and careful perioperative monitoring. In the past decade, two influential randomized trials found that treatment with beta-blockers can decrease the incidence of myocardial infarction and death after noncardiac surgery.[10,11] Because they appear efficacious, are inexpensive, and have few risks, beta-blockers are now widely advocated.[12-16] In *Making Health Care Safer*, the Agency for Healthcare Research and Quality identified the perioperative use of beta-blockers among intermediate- and high-risk patients as one of the nation's "clear opportunities for safety improvement."[17] The National Quality Forum subsequently placed the use of beta-blockers among high-risk surgical patients on its list of 30 *Safe Practices for Better Healthcare*.[18] Yet, two recent randomized trials[19-21] reported no benefit from perioperative beta-blocker therapy and raised questions about the generalizability of earlier studies. While awaiting the results of large randomized trials,[22] we evaluated the use and effectiveness of perioperative beta-blocker therapy in routine clinical practice.

METHODS

SETTING AND SUBJECTS

We conducted a retrospective cohort study using data from 329 hospitals that participate in Premier's Perspective, a database developed for measuring quality and use of health care. Participating hospitals represent all regions of the United States, are predominantly small-to-mid-size nonteaching facilities, and serve a largely urban patient population. In addition to the information available in the standard hospital-discharge file, the Perspective database contains a date-stamped log of all billed items, including medications and laboratory, diagnostic, and therapeutic services, for each patient.

Patients were included in our database if they were 18 years of age or older and had undergone major noncardiac surgery between January 1, 2000, and December 31, 2001. Surgical procedures were categorized with the use of APR-DRG software (version 15.0, 3M) and, on the basis of prior studies, were considered major if the median length of stay for patients in a given diagnosis-related group exceeded two days.[9] Patients undergoing obstetrical procedures were excluded. Permission to conduct the study was granted by the institutional review board at Baystate Medical Center, where the study was conducted, and the need for written informed consent was waived.

DATA ELEMENTS

For each patient, we noted the type of surgery, whether the admission was elective or emergency, and the hospital at which the operation took place. In addition to age, sex, and race or ethnic group, we recorded the presence or absence of known ischemic heart disease, congestive heart failure, cerebrovascular disease, hypertension, renal insufficiency, diabetes, and hyperlipidemia. The presence or absence of coexisting conditions was assessed with the use of the secondary diagnoses of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Furthermore, we considered a patient to have diabetes if there was a secondary diagnosis of diabetes mellitus or if the patient received treatment with an oral hypoglycemic agent during the hospitalization. In a secondary analysis, we expanded our definition of diabetes to include patients who were treated with insulin whether or not they received oral hypoglycemic agents or had a documented diagnosis of diabetes.

Perioperative administration of angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, antiplatelet agents, lipid-lowering medications, loop diuretics, thiazide diuretics, antiarrhythmic agents, and dopamine or dobutamine was assessed with the use of pharmacy records. Information on prophylactic antibiotic administration and the use of pharmacologic and mechanical measures for the prevention of venous thromboembolism was gathered simi-

Table 1. Characteristics of Patients Undergoing Major Noncardiac Surgery without Known Contraindications to Beta-Blockers, According to Whether They Received Beta-Blockers Perioperatively.*

Characteristic	All Patients (N=663,635)	Patients Given Beta-Blockers (N=122,338)	Patients Not Given Beta-Blockers (N=541,297)†	Rate of Use of Beta-Blockers	Odds Ratio for Perioperative Treatment (95% CI)
				%	
Age					
Median — yr	62	68	60		
Interquartile range	47–74	56–76	46–73		
<65 yr — no. (%)‡	359,282 (54)	50,507 (41)	308,775 (57)	14.1	1.00
≥65 yr — no. (%)	304,353 (46)	71,831 (59)	232,522 (43)	23.6	1.89 (1.87–1.91)
Sex — no. (%)§					
Male‡	304,795 (46)	57,381 (47)	247,414 (46)	18.8	1.00
Female	358,824 (54)	64,954 (53)	293,870 (54)	18.1	0.95 (0.94–0.97)
Race or ethnic group — no. (%)¶					
White‡	449,765 (68)	85,153 (70)	364,612 (67)	18.9	1.00
Black	71,587 (11)	13,490 (11)	58,097 (11)	18.8	0.99 (0.97–1.01)
Hispanic	26,203 (4)	4,122 (3)	22,081 (4)	15.7	0.80 (0.77–0.83)
Asian	9,696 (1)	1,528 (1)	8,168 (2)	15.8	0.80 (0.76–0.85)
Other or American Indian	106,384 (16)	18,045 (15)	88,339 (16)	17.0	0.87 (0.86–0.89)
Medical history — no. (%)					
Hypertension	255,498 (38)	77,366 (63)	178,132 (33)	30.3	3.51 (3.46–3.55)
Diabetes‖	113,425 (17)	30,323 (25)	83,102 (15)	26.7	1.82 (1.79–1.84)
Diabetes (expanded definition)**	137,919 (21)	35,307 (29)	102,612 (19)	25.6	1.73 (1.71–1.76)
Ischemic heart disease	86,171 (13)	35,352 (29)	50,819 (9)	41.0	3.92 (3.86–3.98)
Renal insufficiency	26,377 (4)	8,224 (7)	18,153 (3)	31.2	2.08 (2.02–2.13)
Hyperlipidemia	31,535 (5)	9,726 (8)	21,809 (4)	30.8	2.06 (2.01–2.11)
Cerebrovascular disease	8,947 (1)	3,089 (3)	5,858 (1)	34.5	2.37 (2.27–2.47)
Type of procedure — no. (%)					
Vascular‡	51,095 (8)	15,793 (13)	35,302 (7)	30.9	1.00
Orthopedic	245,571 (37)	47,035 (38)	198,536 (37)	19.2	0.53 (0.52–0.54)
Abdominal	222,268 (33)	33,700 (28)	188,568 (35)	15.2	0.40 (0.39–0.41)
Thoracic	47,730 (7)	10,317 (8)	37,413 (7)	21.6	0.62 (0.60–0.63)
Other	96,971 (15)	15,493 (13)	81,478 (15)	16.0	0.43 (0.41–0.44)
Type of admission — no. (%)					
Elective‡	343,718 (52)	66,159 (54)	277,559 (51)	19.2	1.00
Urgent	115,871 (17)	21,380 (17)	94,491 (17)	18.5	0.95 (0.93–0.97)
Emergency	204,046 (31)	34,799 (28)	169,247 (31)	17.1	0.86 (0.85–0.88)
RCRI score — no. (%)††					
0‡	329,171 (50)	47,261 (39)	281,910 (52)	14.4	1.00
1	251,494 (38)	47,116 (39)	204,378 (38)	18.7	1.38 (1.36–1.39)
2	67,955 (10)	21,972 (18)	45,983 (8)	32.3	2.85 (2.80–2.90)
3	13,744 (2)	5,433 (4)	8,311 (2)	39.5	3.90 (3.76–4.04)
≥4	1,271 (<1)	556 (<1)	715 (<1)	43.7	4.64 (4.15–5.18)

Table 1. (Continued.)

Characteristic	All Patients (N=663,635)	Patients Given Beta-Blockers (N=122,338)	Patients Not Given Beta-Blockers (N=541,297)†	Rate of Use of Beta-Blockers	Odds Ratio for Perioperative Treatment (95% CI)
				%	
Expanded RCRI score — no. (%)‡‡					
0‡	317,969 (48)	45,239 (37)	272,730 (50)	14.2	1.00
1	251,612 (38)	46,932 (38)	204,680 (38)	18.7	1.38 (1.36–1.40)
2	76,983 (12)	23,488 (19)	53,495 (10)	30.5	2.65 (2.60–2.70)
3	15,655 (2)	6,060 (5)	9,595 (2)	38.7	3.81 (3.68–3.93)
≥4	1,416 (<1)	619 (<1)	797 (<1)	43.7	4.68 (4.21–5.20)
High-risk surgery — no. (%)	198,826 (30)	32,603 (27)	166,223 (31)	16.4	0.82 (0.81–0.83)
Type of insurance — no. (%)					
Medicare‡	300,135 (45)	69,949 (57)	230,186 (43)	23.3	1.00
Private	267,131 (40)	40,848 (33)	226,283 (42)	15.3	0.59 (0.58–0.60)
Medicaid	35,175 (5)	4,705 (4)	30,470 (6)	13.4	0.51 (0.49–0.52)
Uninsured	24,467 (4)	2,100 (2)	22,367 (4)	8.6	0.31 (0.30–0.32)
Other	36,727 (6)	4,736 (4)	31,991 (6)	12.9	0.49 (0.47–0.50)
Medications — no. (%)					
Antibiotics	405,622 (61)	77,737 (64)	327,885 (61)	19.2	1.13 (1.12–1.15)
DVT prophylaxis					
Pharmacologic	227,364 (34)	53,670 (44)	173,694 (32)	23.6	1.65 (1.63–1.68)
Mechanical	240,160 (36)	46,270 (38)	193,890 (36)	19.3	1.09 (1.08–1.10)
Lipid-lowering agents	62,221 (9)	25,170 (21)	37,051 (7)	40.4	3.53 (3.46–3.59)
Calcium-channel blockers	89,476 (13)	27,923 (23)	61,553 (11)	31.2	2.31 (2.27–2.34)
ACE inhibitor	76,382 (12)	25,522 (21)	50,860 (9)	33.4	2.54 (2.50–2.58)
Antiplatelet agents	65,923 (10)	23,574 (19)	42,349 (8)	35.8	2.81 (2.76–2.86)
Loop diuretics	76,084 (11)	23,896 (20)	52,188 (10)	31.4	2.28 (2.24–2.31)
Angiotensin-receptor blockers	18,613 (3)	6,365 (5)	12,248 (2)	34.2	2.37 (2.30–2.45)
Thiazide	21,625 (3)	7,304 (6)	14,321 (3)	33.8	2.34 (2.27–2.40)
Antiarrhythmic	6,650 (1)	2,169 (2)	4,481 (1)	32.6	2.16 (2.05–2.28)
Dopamine or dobutamine	14,815 (2)	4,101 (3)	10,714 (2)	27.7	1.72 (1.66–1.78)
Type of hospital — no. (%)					
Nonteaching‡	521,470 (79)	93,142 (76)	428,328 (79)	17.9	1.00
Teaching	142,165 (21)	29,196 (24)	112,969 (21)	20.5	1.19 (1.17–1.21)
No. of beds in hospital — no. (%)					
1–200‡	87,640 (13)	13,089 (11)	74,551 (14)	14.9	1.00
201–400	225,809 (34)	41,050 (34)	184,759 (34)	18.2	1.27 (1.24–1.29)
401–600	180,622 (27)	33,653 (28)	146,969 (27)	18.6	1.30 (1.28–1.33)
601–800	119,065 (18)	22,323 (18)	96,742 (18)	18.8	1.31 (1.28–1.35)
801–1000	50,499 (8)	12,223 (10)	38,276 (7)	24.2	1.82 (1.77–1.87)

Table 1. (Continued.)

Characteristic	All Patients (N=663,635)	Patients Given Beta-Blockers (N=122,338)	Patients Not Given Beta-Blockers (N=541,297)†	Rate of Use of Beta-Blockers	Odds Ratio for Perioperative Treatment (95% CI)
				%	
Region — no. (%)					
South‡	373,033 (56)	69,563 (57)	303,470 (56)	18.7	1.00
Northeast	45,065 (7)	9,806 (8)	35,259 (7)	21.8	1.21 (1.18–1.24)
Midwest	160,397 (24)	30,577 (25)	129,820 (24)	19.1	1.03 (1.01–1.04)
West	85,140 (13)	12,392 (10)	72,748 (13)	14.6	0.74 (0.73–0.76)
Population served by hospital — no. (%)					
Rural‡	111,078 (17)	18,917 (15)	92,161 (17)	17.0	1.00
Urban	552,557 (83)	103,421 (85)	449,136 (83)	18.7	1.12 (1.10–1.14)
In-hospital mortality — no. (%)	13,454 (2)	2,839 (2)	10,615 (2)	21.1	
Length of stay — days					
Median	5	5	5		
Interquartile range	3–8	3–8	3–8		
Cost — $					
Median	8,537	9,419	8,333		
Interquartile range	5,472–13,236	6,182–14,411	5,332–12,956		

* CI denotes confidence interval, RCRI Revised Cardiac Risk Index, DVT deep venous thrombosis, and ACE angiotensin-converting enzyme.
† Patients who received beta-blockers after the second hospital day were included in the group that did not receive beta-blockers.
‡ This group served as the reference group.
§ Information about sex was missing for 16 patients.
¶ Race or ethnic group was self-assigned.
‖ Diabetes was defined on the basis of the secondary diagnoses of the ICD-9-CM code or the in-hospital use of an oral hypoglycemic agent.
** The expanded definition of diabetes was based on the secondary diagnoses of the ICD-9-CM code or the in-hospital use of an oral hypoglycemic agent or insulin.
†† The primary definition of diabetes was used.
‡‡ The expanded definition of diabetes was used.

larly. Data on in-hospital mortality, length of stay, and costs were obtained from the Perspective discharge file. In addition to information related to the admission, we noted each hospital's size, teaching status, and geographic location and whether it was urban or rural.

Adapting a classification scheme developed by Lee and colleagues, we calculated a Revised Cardiac Risk Index (RCRI) score for each patient, assigning one point for each of the following risk factors: high-risk surgery, ischemic heart disease, cerebrovascular disease, renal insufficiency, and diabetes mellitus.[9] The category of high-risk surgery included all intrathoracic, intraperitoneal, and suprainguinal vascular procedures. Patients were excluded if they had received a secondary diagnosis that could be considered a contraindication to beta-blocker therapy; these included bradycardia, heart block, heart failure, hypotension, chronic obstructive pulmonary disease, and asthma.

USE OF BETA-BLOCKERS

We identified whether a beta-blocker had been administered either orally or intravenously at any time during the hospitalization, and if so, the date the medication was first administered. Because we lacked information about the date of the principal procedure as well as the goals of the ordering physicians, we considered a patient to have received beta-blocker therapy for prophylaxis, whether intentionally or not, if the first record of treatment occurred on the first or second hospital day. Patients who had treatment initiated on the third hospital day or later were grouped with those who did not receive a beta-blocker during the hospitalization, since this former group may have had therapy pre-

Table 2. Characteristics of the 329 Hospitals.*

Characteristic	Hospitals (N=329)	Patients (N=663,635)	Mortality Rate	Rate of Use of Beta-Blockers
	number (percent)		*percent*	
Type of hospital				
Nonteaching	296 (90)	521,470 (79)	1.7±1.0	16.0±7.0
Teaching	33 (10)	142,165 (21)	4.1±10.5	18.4±8.0
No. of beds in hospital				
1–200	134 (41)	87,640 (13)	1.5±1.2	13.9±7.7
201–400	112 (34)	225,809 (34)	1.9±0.8	17.6±5.7
401–600	54 (16)	180,622 (27)	2.3±0.7	17.7±6.9
601–800	23 (7)	119,065 (18)	4.9±12.5	18.3±5.6
801–100	6 (2)	50,499 (8)	2.1±0.5	23.9±7.6
Region				
South	176 (53)	373,033 (56)	2.2±4.6	16.5±6.2
Midwest	76 (23)	160,397 (24)	1.6±0.9	17.5±8.3
West	56 (17)	85,140 (13)	1.7±1.1	12.8±6.4
Northeast	21 (6)	45,065 (7)	2.0±1.3	19.4±8.2
Population served				
Urban	224 (68)	552,557 (83)	2.2±4.2	17.0±7.0
Rural	105 (32)	111,078 (17)	1.6±0.9	14.7±7.1

* Plus–minus values are means ±SD.

scribed for the treatment of complications rather than for their prevention.

STATISTICAL ANALYSIS

Summary statistics were constructed with the use of frequencies and proportions for categorical data and means, medians, and interquartile ranges for continuous variables. We compared the characteristics of patients who received perioperative beta-blocker therapy during the first two hospital days with those who did not receive beta-blockers during the first two days. Chi-square and z tests were used to assess the relationship between treatment with beta-blockers and the risk of death in the hospital and any potential confounders.

We created a nonparsimonious logistic-regression model to derive a propensity score for early treatment with beta-blockers that included all patient and hospital characteristics as well as selected interaction terms. Each patient was assigned a propensity score that reflected the probability that they would receive early treatment. Using a Greedy 5-to-1 digit-matching algorithm,[23] we matched each patient who received perioperative beta-blocker therapy with up to two patients who did not receive this therapy, starting with all five-digit propensity-score matches before moving to those with four or fewer matches, in an iterative process. These matching techniques were used to reduce bias introduced by incomplete or inexact matching.

The matched cohort was evaluated for differences between treatment groups in each of the potential confounding factors, and conditional logistic regression was used to assess the effect of beta-blockers on the risk of death in the hospital, after adjustment for any residual differences (given a P value of less than 0.01). Using both the matched and entire study cohorts, we examined the association between beta-blocker therapy and the risk of death in the hospital among patients on the basis of the RCRI score. In addition, in the entire study cohort we evaluated models for selected subpopulations, including patients with hypertension and an RCRI score of 0 and patients with an RCRI score of 1 and each of the individual RCRI factors. Interactions between beta-blocker treatment and unbal-

anced covariates were also evaluated for each model and retained if the resulting P value was less than 0.05. The Hosmer–Lemeshow goodness-of-fit test and the area under the curve were used to assess the fit of the model. All analyses were carried out with the use of SAS software (version 9.1).

RESULTS

A total of 782,969 patients 18 years of age or older underwent major noncardiac surgery during the study period. Among this group, 119,334 (15 percent) had one or more documented potential contraindications to beta-blockade. Thus, 663,635 patients appeared to be eligible for perioperative treatment with beta-blockers. The median age was 62 years; slightly more than half were women, and two thirds were white (Table 1). Hypertension, diabetes, and ischemic heart disease were the most common coexisting conditions. Fifty percent had an RCRI score of 0, and 38 percent had an RCRI score of 1.

In the secondary analysis, using the expanded definition of diabetes, we identified an additional 4 percent of the population as having this diagnosis; the additional patients classified as having diabetes shifted RCRI scores upward slightly. Orthopedic and abdominal operations accounted for 70 percent of procedures, 30 percent of the procedures were categorized as high risk, and just over half the admissions were elective. The median length of stay was five days. Overall, 13,454 eligible patients (2.0 percent) died during the hospitalization: 2839 of the 122,338 patients who received early treatment with beta-blockers (2.3 percent) and 10,615 of the 541,297 patients who did not receive beta-blockers or received them after the second hospital day (2.0 percent, P<0.001).

The majority of participating hospitals were in the South. Seventy-five percent had a capacity of 400 beds or less, 90 percent were nonteaching facilities, and 68 percent were in urban areas (Table 2).

USE OF BETA-BLOCKERS AMONG PATIENTS UNDERGOING MAJOR NONCARDIAC SURGERY

Of the 663,635 eligible patients, 122,338 (18 percent) received a beta-blocker on the first or second day of the hospitalization. Women were less likely than men to receive beta-blockers, and Hispanics, Asians, and other racial or ethnic groups were treated less frequently than whites and blacks (Table 1). A history of ischemic heart disease, a higher RCRI score, and hypertension were the characteristics most strongly associated with beta-blocker treatment. Treatment rates ranged from 14 percent among patients with an RCRI score of 0 to 44 percent among those with a score of 4 or higher. Patients whose operations were scheduled electively had higher rates of beta-blocker use than those whose procedures were classified as urgent or emergency, and patients who underwent vascular surgery were more likely to receive beta-blockers than were those undergoing other types of procedures. Hospitals located in the Northeast that served urban populations, had a bed capacity of at least 200, and were designated teaching hospitals were more likely to deliver beta-blocker therapy than were other types of hospitals.

BETA-BLOCKER THERAPY AND IN-HOSPITAL MORTALITY

Sixteen patients were excluded from multivariable modeling owing to missing data. We successfully matched 119,632 patients (98 percent) who received a beta-blocker in the early perioperative period with at least 1 patient who did not receive a beta-blocker or received it after the second hospital day (79 percent with two matches and 19 percent with one match) on the basis of the propensity score. In this propensity-matched cohort (Table 3), 2790 of 119,632 patients treated with beta-blockers died, as compared with 5123 of 216,290 patients who did not receive such therapy or who received it after the second hospital day (2.3 percent vs. 2.4 percent; match-adjusted odds ratio, 0.99; 95 percent confidence interval, 0.95 to 1.04; P=0.68).

The preoperative RCRI score significantly modified the association between beta-blocker treatment and the risk of death in the hospital. Among the subgroup of patients included in the propensity analysis, early beta-blocker treatment was associated with a reduced risk of death among patients with scores of 3 or higher (Fig. 1), with odds ratios ranging from 1.43 (95 percent confidence interval, 1.29 to 1.58) among patients in the lowest RCRI category to 0.57 (95 percent confidence interval, 0.42 to 0.76) among those with an RCRI score of 4 or higher.

Similar results were observed in the entire study cohort, except that a significant benefit of treatment was also observed among patients with an RCRI score of 2 (Fig. 1). In a subgroup analysis of patients who had an RCRI score of 0 and hypertension, the odds ratio of death in the hospital was

Table 3. Characteristics of the Patients Who Received Beta-Blockers Perioperatively and Those Who Did Not Receive Such Therapy in the Propensity-Matched Cohort.*

Characteristic	Beta-Blockers (N=119,632)	No Beta-Blockers (N=216,290)	P Value
Age — yr			<0.001
Median	68	68	
Interquartile range	56–76	57–77	
Female sex — no. (%)	63,866 (53)	118,034 (55)	<0.001
Race or ethnic group — no. (%)			0.003
White	83,130 (69)	148,946 (69)	
Black	13,234 (11)	24,583 (11)	
Hispanic	4,038 (3)	7,338 (3)	
Asian	1,503 (1)	2,692 (1)	
Other or American Indian	17,727 (15)	32,731 (15)	
Medical history — no. (%)			
Hypertension	74,743 (62)	132,691 (61)	<0.001
Diabetes	29,128 (24)	50,303 (23)	<0.001
Ischemic heart disease	32,793 (27)	44,600 (21)	<0.001
Renal insufficiency	7,861 (7)	13,291 (6)	<0.001
Hyperlipidemia	9,198 (8)	14,439 (7)	<0.001
Cerebrovascular disease	2,846 (2)	4,329 (2)	<0.001
Type of procedure — no. (%)			<0.001
Orthopedic	46,253 (39)	85,657 (40)	
Abdominal	33,297 (28)	62,388 (29)	
Thoracic	10,004 (8)	17,630 (8)	
Vascular	14,913 (12)	23,629 (11)	
Other	15,165 (13)	26,986 (12)	
Type of admission — no. (%)			0.888
Elective	64,610 (54)	116,996 (54)	
Urgent	20,885 (17)	37,719 (17)	
Emergency	34,137 (29)	61,575 (28)	
RCRI score — no. (%)			<0.001
0	47,216 (39)	94,700 (44)	
1	46,121 (39)	81,231 (38)	
2	20,825 (17)	32,413 (15)	
3	4,996 (4)	7,264 (3)	
≥4	474 (0.4)	682 (<1)	
High-risk surgery — no. (%)	32,035 (27)	58,067 (27)	0.666
Type of insurance — no. (%)			0.001
Medicare	68,295 (57)	124,351 (57)	
Private	39,958 (33)	71,928 (33)	
Medicaid	4,610 (4)	8,215 (4)	
Uninsured	2,086 (2)	3,392 (2)	
Other	4,683 (4)	8,404 (4)	

Table 3. (Continued.)

Characteristic	Beta-Blockers (N=119,632)	No Beta-Blockers (N=216,290)	P Value
Medications — no. (%)†			
Antibiotics	76,026 (64)	137,844 (64)	<0.001
VTE prophylaxis			
Pharmacologic	51,978 (43)	91,444 (42)	<0.001
Mechanical	45,433 (38)	84,459 (39)	<0.001
Lipid-lowering agents	22,989 (19)	31,350 (14)	<0.001
Calcium-channel blockers	26,767 (22)	45,330 (21)	<0.001
ACE inhibitor	24,202 (20)	39,565 (18)	<0.001
Antiplatelet agents	21,794 (18)	31,508 (15)	<0.001
Loop diuretics	22,632 (19)	36,220 (17)	<0.001
Angiotensin-receptor blockers	6,027 (5)	9,712 (4)	<0.001
Thiazide diuretics	6,988 (6)	11,705 (5)	<0.001
Antiarrhythmic agents	2,061 (2)	3,244 (1)	<0.001
Dopamine or dobutamine	3,923 (3)	6,555 (3)	<0.001
Type of hospital — no. (%)			0.002
Nonteaching	91,323 (76)	166,140 (77)	
Teaching	28,309 (24)	50,150 (23)	
No. of beds in hospital — no. (%)			<0.001
1–200	12,975 (11)	24,549 (11)	
201–400	40,219 (34)	72,698 (34)	
401–600	32,903 (28)	59,367 (27)	
601–800	21,873 (18)	39,988 (18)	
801–1000	11,662 (10)	19,688 (9)	
Region — no. (%)			<0.001
South	67,921 (57)	122,722 (57)	
Midwest	29,947 (25)	53,876 (25)	
West	12,287 (10)	23,087 (11)	
Northeast	9,477 (8)	16,605 (8)	
Population served — no. (%)			0.018
Urban	101,035 (84)	181,994 (84)	
Rural	18,597 (16)	34,296 (16)	
In-hospital mortality — no. (%)	2,790 (2)	5,123 (2)	0.505
Length of stay — days			0.004
Median	5	5	
Interquartile range	3–8	3–8	
Cost — $			<0.001
Median	9,404	9,082	
Interquartile range	6,769–14,389	6,019–13,703	

* The propensity-matched cohort consisted of 119,632 patients who had received a beta-blocker perioperatively, each of whom was matched with either 1 or 2 patients who had not received such therapy. Analyses used the primary definition of diabetes mellitus. Patients who received beta-blockers after the second hospital day were included in the group that did not receive beta-blockers.

† VTE denotes venous thromboembolism, RCRI Revised Cardiac Risk Index, and ACE angiotensin-converting enzyme.

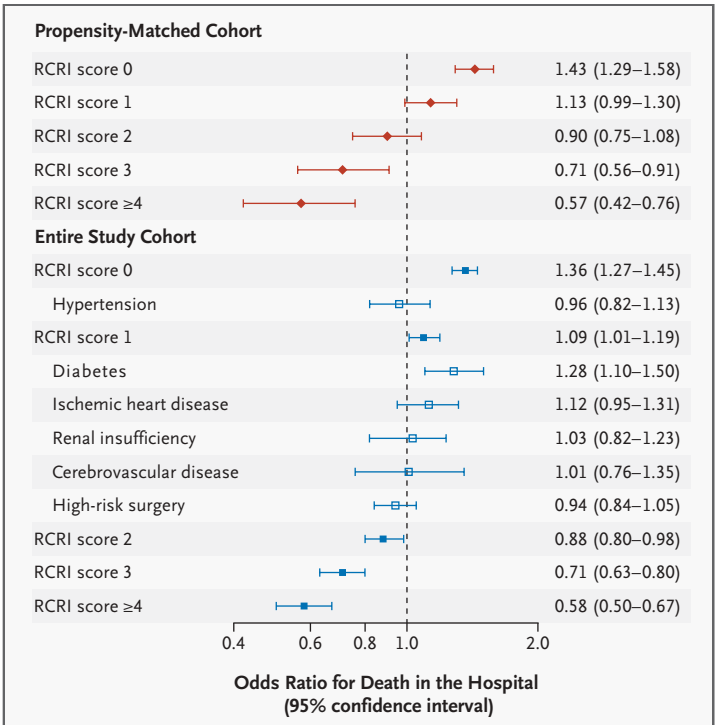

Figure 1. Adjusted Odds Ratio for In-Hospital Death Associated with Perioperative Beta-Blocker Therapy among Patients Undergoing Major Noncardiac Surgery, According to the RCRI Score and the Presence of Other Risk Factors in the Propensity-Matched Cohort and the Entire Study Cohort.

Open boxes represent patient subgroups within the listed RCRI category.

0.96 (95 percent confidence interval, 0.82 to 1.13) among those who received beta-blockers early, as compared with those who did not receive them. Furthermore, among patients with an RCRI score of 1, we found no reduction in the risk of death in the hospital related to beta-blocker use in any subpopulation. On the basis of these results, the number needed to treat to prevent a single death in the hospital was 33 among those at highest risk, whereas, in instances in which the risk was increased with beta-blocker use, the number needed to harm (i.e., the number of patients who would need to be treated for a single death in the hospital to occur) was 208 among the lowest-risk patients, who were least likely to receive treatment with beta-blockers (Table 4).

In a secondary analysis, using the expanded definition of diabetes, we observed generally similar results; however, the benefits of beta-blocker therapy were attenuated and were no longer significant for patients with an RCRI score of 2 (results are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DISCUSSION

Although evidence from randomized trials remains limited, the treatment of surgical patients with beta-blockers has been championed by clinicians and policymakers for its potential to enhance patient safety. In this large observational study, the perioperative administration of beta-blockers was associated with clear and clinically significant reductions in mortality among the 2 percent of surgical patients at highest risk (those with an RCRI score of 3 or greater) and appeared to be beneficial in the 10 percent of patients with an RCRI score of 2, but was of no benefit — and was possibly harmful — among patients in the lowest risk categories (those with an RCRI score of 0 or 1). Our observation that only a minority of patients at highest risk received beta-blockers underscores the Agency for Healthcare Research and Quality's statement that perioperative use of beta-blockade represents a clear opportunity for safety improvement.[17]

Two randomized trials have shown that the use of beta-blockers decreases the risk of death among surgical patients. The Multicenter Study of Perioperative Ischemia Research Group[10] randomly assigned 200 male veterans with known coronary artery disease or two or more coronary risk factors to receive atenolol or placebo before undergoing major noncardiac surgery and reported that within several months after discharge, treated patients had a significant survival advantage. Poldermans et al.[11] randomly assigned 112 patients with abnormal stress echocardiograms to receive bisoprolol or placebo before and after vascular surgery and found a marked reduction in the risk of myocardial infarction and death during hospitalization and at 30 days postoperatively.

Two recently completed trials have, however, raised questions about the generalizability of the earlier studies. In the first, patients undergoing vascular surgery who were randomly assigned to receive metoprolol had rates of major cardiovascular complications or death from cardiac causes at 30 days that were similar to the rates among those who received placebo.[19] In the second, 921 patients with diabetes who were randomly assigned to receive metoprolol or placebo[20,21] had similar rates of a composite end point of death from any cause or major cardiovascular complications after a median follow-up of 18 months. It is unclear whether the lack of benefit in these recent trials can be explained by differences in treatment protocols or by lower-than-expected rates of events, which would

Table 4. Rates and Risks of In-Hospital Death and the Numbers Needed to Treat and to Harm among Patients in the Entire Study Cohort Who Did Not Receive Perioperative Beta-Blockade, According to the RCRI Score and the Presence of Individual Risk Factors.*

Subgroup	Mortality Rate	Odds Ratio (95% CI)	No. Needed to Treat (95% CI)	No. Needed to Harm (95% CI)
	%			
RCRI score, 0				
All patients	1.4	1.36 (1.27–1.45)	—	208 (276–164)
Patients with hypertension	1.2	0.96 (0.82–1.13)	2349 (496–637)†	
RCRI score, 1				
All patients	2.2	1.09 (1.01–1.19)		504 (4937–256)
Patients with diabetes	1.7	1.28 (1.10–1.50)		209 (583–117)
Patients with ischemic heart disease	2.0	1.12 (0.95–1.31)		408 (975–158)‡
Patients with cerebrovascular disease	9.0	1.03 (0.82–1.23)		410 (67–54)‡
Patients with renal insufficiency	7.2	1.01 (0.76–1.35)		1505 (62–44)‡
Patients undergoing high-risk surgery	2.0	0.94 (0.84–1.05)	864 (323–1039)†	
RCRI score, 2				
All patients	3.9	0.88 (0.80–0.98)	227 (132–1091)	
RCRI score, 3				
All patients	5.8	0.71 (0.63–0.80)	62 (48–92)	
RCRI score, ≥4				
All patients	7.4	0.58 (0.50–0.67)	33 (28–42)	

* Analyses used the primary definition of diabetes. Results using the expanded definition of diabetes are provided in the Supplementary Appendix. The number needed to treat is the number of patients who would need to be treated to prevent one death; the number needed to harm is the number of patients who would need to be treated for one death to occur. CI denotes confidence interval.
† The upper limit of the confidence interval is actually the number needed to harm.
‡ The lower limit of the confidence interval is actually the number needed to treat.

have reduced the statistical power of the studies to detect a moderate effect of treatment.

By evaluating the effect of beta-blocker therapy in a diverse population undergoing a wide variety of surgical procedures at more than 300 hospitals throughout the United States, our results extend the findings from these earlier studies and provide support for the perioperative use of beta-blockers in high-risk patients, while we await the results of a large, ongoing, randomized trial.[22] Yet the lack of benefit of this approach in moderate-risk patients and the potential harm of this approach in the lowest-risk groups suggest that careful patient selection remains necessary.

Our study has some limitations. First, treatment with beta-blockers was not based on random assignment, and results may be confounded by other variables. Although we used rigorous statistical methods to adjust for baseline differences between patients, including propensity-score matching and stratification, the retrospective nature of the study meant that our ability to control for differences was limited to variables for which data were available. Furthermore, because we relied on claims data, the ascertainment of coexisting conditions and potential contraindications to beta-blocker treatment was dependent on physicians' documentation and hospitals' coding practices. Although previous studies have validated the use of administrative data for these purposes,[24,25] they also suggest that we may have underestimated the prevalence of some coexisting conditions. We noted that a substantially greater number of patients were classified as having diabetes when we added insulin use as a diag-

nostic criterion in the absence of an ICD-9-CM code for diabetes. Insofar as we underestimated the prevalence of coexisting conditions, our effect estimates among lower-risk patients may be overly optimistic, whereas the percentage of the population that might actually benefit from beta-blockers could be larger than the 2 to 12 percent we forecast.

An additional limitation was that our study was restricted to the period of hospitalization. We did not have access to information about the use of beta-blockers before admission or after discharge and were unable to report 30-day or 1-year mortality rates. Nevertheless, other trials of perioperative beta-blocker therapy have used protocols in which treatment was begun only hours before surgery and have generally relied on longer-term outcomes because they have been statistically underpowered to detect short-term differences.[10,19-21] Furthermore, we presumed that patients who were treated with a beta-blocker on the first or second hospital day were given the drug for prophylaxis; however, it is likely that some of these patients were actually given beta-blockers for the treatment of postoperative ischemia or infarction. Such misclassification was more likely among the lowest-risk patients, who were least likely to receive prophylaxis. To the extent that we misclassified patients in this way, our results would underestimate the effectiveness of beta-blocker therapy or would incorrectly suggest that beta-blockers were harmful.

Without access to patients' charts, we could not determine the effect of beta-blocker treatment on heart rates before, during, or after surgery. Finally, because administrative data are not a reliable source of information about postoperative cardiovascular complications,[26] we were unable to report the incidence of ischemia or infarction.

We found that perioperative administration of beta-blockers was associated with a reduced risk of death in the hospital among high-risk patients undergoing major noncardiac surgery. Thus, until the results of large randomized trials become available, ongoing national efforts to increase patient safety by increasing the perioperative use of beta-blockers among high-risk patients appear warranted.

Presented at the annual meeting of the Society of General Internal Medicine, Vancouver, B.C., Canada, May 1, 2003.

We are indebted to Andrew Auerbach, M.D., M.P.H., and Michael Rothberg, M.D., M.P.H., for their comments on an earlier version of the manuscript.

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BRIEF REPORT

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease

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SUMMARY

The prior diagnosis of fatal astrocytoma in a 60-year-old man with Crohn's disease treated with natalizumab, a monoclonal antibody against α_4 integrins, was reclassified as JC virus–related progressive multifocal leukoencephalopathy (PML). Analysis of frozen serum samples showed that JC virus DNA had appeared in the serum three months after the initiation of open-label natalizumab monotherapy and two months before the appearance of symptomatic PML. There was staining of the brain lesion for polyomavirus. This case report, along with two others, suggests that anti–α_4-integrin therapy can result in JC virus–induced PML.

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This article was published at www.nejm.org on June 9, 2005.

N Engl J Med 2005;353:362-8.

NATALIZUMAB HAS GREAT THERAPEUTIC POTENTIAL IN BOTH MULTIPLE sclerosis and inflammatory bowel disease.[1-3] Two cases of progressive multifocal leukoencephalopathy (PML) have recently been reported in patients with multiple sclerosis who were treated with a humanized monoclonal antibody against α_4 integrins, natalizumab (Tysabri, Elan and Biogen Idec), in combination with interferon beta-1a (Avonex, Biogen Idec).[4] One of these cases is described elsewhere in this issue of the *Journal*.[5] We report a third case of PML — this one in a patient with Crohn's disease who received 300 mg of open-label natalizumab intravenously every four weeks as part of a clinical trial. PML is an opportunistic, infectious, demyelinating brain disorder associated with impaired T-cell function. The relationship between natalizumab therapy and PML in our patient is clearly illustrated by the gradual increase in the number of copies of JC virus in the blood during monotherapy in the months preceding the development of fatal PML.

CASE REPORT

A 60-year-old patient with long-standing ileal Crohn's disease presented to the emergency unit with severe confusion and disorientation on July 3, 2003. Treatment with natalizumab, a humanized monoclonal antibody against α_4 integrins, had been initiated in March 2002. He had initially received three monthly infusions of 300 mg intravenously during the Evaluation of Natalizumab as Continuous Therapy 1 (ENACT-1) trial, followed by treatment with placebo for nine months in the ENACT-2 trial. Open-label natalizumab at a dose of 300 mg given intravenously every four weeks was then resumed in

February 2003 for a relapse of Crohn's disease. The patient received five doses of the drug before he was admitted. He had been treated with multiple therapies during that time, including azathioprine (75 to 150 mg given daily), but this treatment had been discontinued eight months before admission because of refractory anemia with low platelet counts and lymphopenia.

Since 1996, the patient had had intermittent signs of deficient hematopoiesis, with lymphopenia and anemia predominating, regardless of ongoing therapy (Fig. 1). A bone marrow smear had shown pancytopenia despite active hematopoiesis, which was interpreted as reflecting chronic inflammatory disease. Since the diagnosis of Crohn's disease 28 years earlier, the patient had been treated with azathioprine, antibiotics, budesonide, and infliximab (with the last infusion given 20 months before admission). Segmental ileal resection had been performed eight and three years earlier.

On admission, the patient was found to be mentally slow, albeit with normal arousal (Mini-Mental State examination score of 29; the highest score is 30). No focal signs were found on neurologic examination. General physical features were also unremarkable, with no fever or abdominal tenderness and with normal vital signs. Routine hematologic and biochemical measurements showed mild iron-deficiency anemia (hemoglobin, 10.7 g per deciliter) with a normal white-cell count and a platelet count of 121,000 per cubic millimeter, a blood glucose level of 150 mg per deciliter (8.3 mmol per liter), a low serum potassium level (3.11 mmol per liter), and a low phosphate level (0.64 mg per deciliter [0.21 mmol per liter]), with otherwise normal serum levels of electrolytes. Levels of C-reactive protein were normal, as were the findings on electrocardiography and chest radiography.

A computed tomographic scan of the brain showed a nonenhancing hypodense lesion in the right frontal lobe. Both T_2-weighted magnetic resonance imaging (MRI) scans and MRI scans obtained with fluid-attenuated inversion recovery revealed hyperintense nonenhancing lesions in the right frontal lobe and in the left frontal and right temporal lobes (Fig. 2).

Because of progressive deterioration in the patient's condition, the decision to perform surgery was made quickly and a spinal tap was not performed. Trephination was performed, with partial

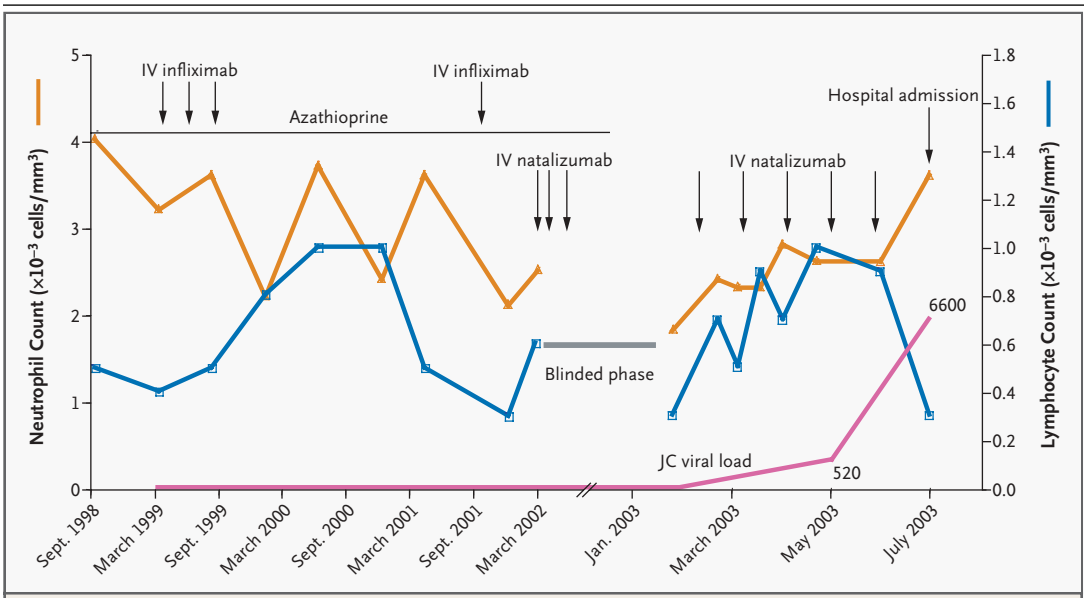

Figure 1. Peripheral-Blood Neutrophil and Lymphocyte Counts in Relation to Natalizumab Therapy.

Values from 1998 to July 2003 are shown, as is the timing of immunomodulatory treatments. Treatment with azathioprine was started before September 1998. Lymphocyte and neutrophil counts were not available during the blinded phase of the ENACT-1 and ENACT-2 trials. JC virus DNA appeared in serum in May 2003, and the viral load (expressed in DNA copies per milliliter) had increased by a factor of 12 by the time of the patient's admission in July 2003. IV denotes intravenous.

resection of the right frontal lesion. Histologic examination showed that the resected lesion mainly contained abnormalities in the white matter, consisting of a mixture of astrocytes with very large and atypical nuclei, lymphocytes, and foamy macrophages (Fig. 3A). Because of the large frontal lesion, the atypical aspect of the nuclei, and the increase in the Ki67-MIB1 proliferation index (±15 percent), a diagnosis of astrocytoma of World Health Organization grade III was made.

The postoperative period was characterized by prolonged confusion and somnolence and seizures, treated with phenytoin. After a temporary improvement in the patient's condition, somnolence and confusion again worsened. MRI performed six weeks after surgery showed enlargement of the lesions in the right temporal and left frontal lobes and mainly postoperative changes in the right frontal lobe (shown in Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Treatment with corticosteroids was initiated, and radiotherapy was planned. However, the patient's condition deteriorated rapidly, and he died three months after the start of corticosteroid therapy, in December 2003. An autopsy was not performed. At its onset, the neurologic syndrome was reported to the manufacturer of natalizumab and to the local institutional review board as a serious adverse event related to therapy.

On March 1, 2005, all investigational and commercial administrations of natalizumab were halted by Elan and Biogen Idec, owing to the occurrence of PML in two patients with multiple sclerosis who had received this drug in combination with interferon beta-1a.[4] This announcement prompted us to reexamine our patient's course, in agreement with Elan and Biogen Idec.

METHODS AND RESULTS

DIAGNOSTIC SPECIMENS

Formalin-fixed and paraffin-embedded tissue was available from the resected brain lesion and from colonic biopsy specimens obtained before the treatment with natalizumab was begun. Also, fresh-frozen surgical samples from a previous ileocolonic resection had been stored at −70°C. Serum samples had been collected and stored at −70°C at regular intervals from 1999 until the detection of the brain lesions, as part of a prospective serum bank for patients with inflammatory bowel disease at our institution. Written informed consent for these collections had been obtained. Samples of cerebrospinal fluid and urine were not available.

PATHOLOGICAL FINDINGS

Reexamination of the brain specimens revealed some oligodendrocyte nuclei with a ground-glass

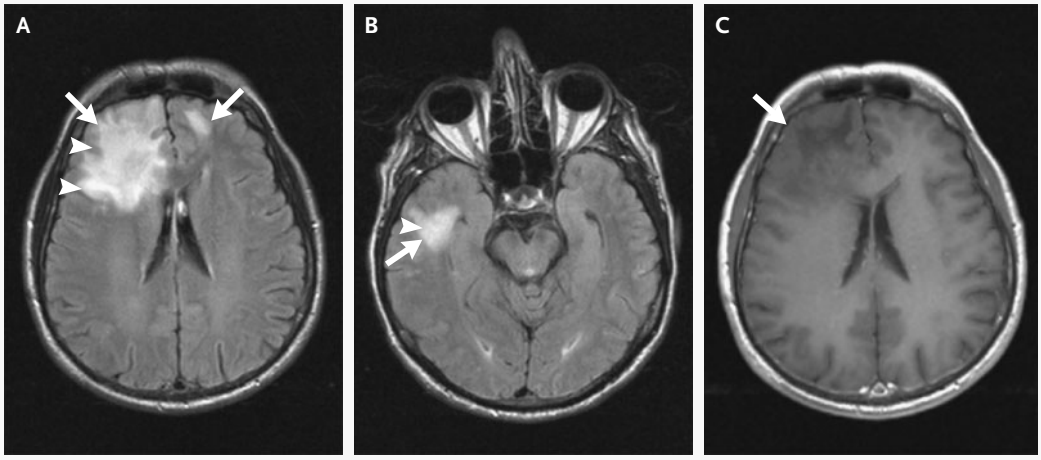

Figure 2. Initial MRI Findings.

In Panel A, a scan obtained with fluid-attenuated inversion recovery reveals a hyperintense lesion in the right frontal lobe and a smaller one in the left frontal region (arrows). A temporal lesion is indicated by the arrow in Panel B. These lesions were mainly confined to the white matter, as shown by the relative sparing of the cortex (arrowheads in Panels A and B), and were not enhanced by the administration of gadolinium on T_1-weighted MRI (Panel C, arrow).

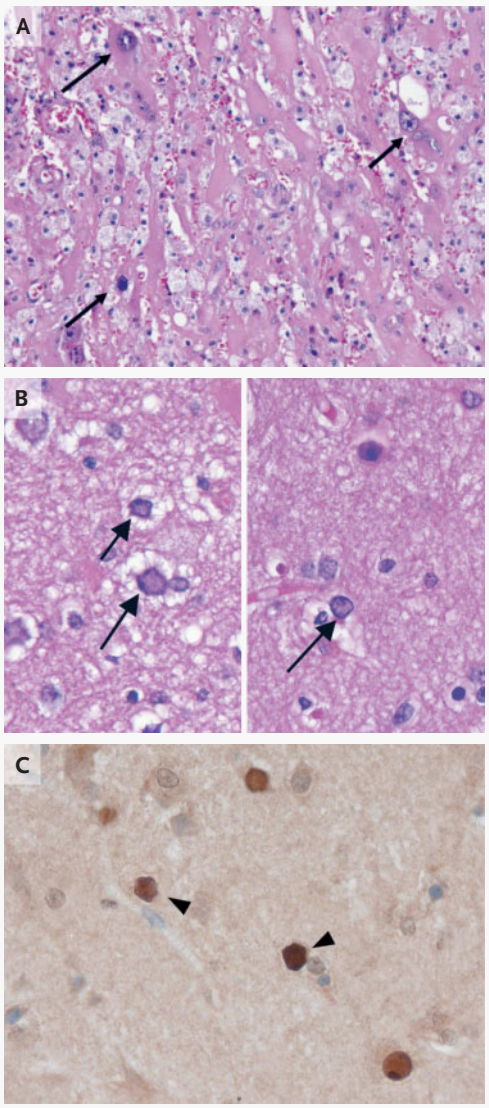

Figure 3. Histologic Findings.

Panel A shows enlarged astrocytes with atypical big nuclei (arrows) intermingled with foamy macrophages (hematoxylin and eosin). Panel B shows ground-glass inclusions of oligodendrocyte nuclei (arrows) (hematoxylin and eosin). Panel C shows rounded oligodendrocyte nuclei stained for polyomavirus antibodies (arrowheads). Immunoreactivity was mainly seen in cortical or subcortical oligodendrocyte nuclei. In the white matter, most of the tissue was destroyed, and staining was mainly seen in the nuclei of atypical astrocytes.

appearance and a basophilic rim of chromatin (Fig. 3B) in the relatively spared cortex, findings suggestive of PML. We then performed immunohistochemical analysis for polyomavirus proteins with mouse monoclonal antibodies directed against the SV40 large T antigen (dilution, 1:10; Oncogene). We used an indirect immunoperoxidase technique (mouse Envision system, DakoCytomation) for detection. Immunohistochemical analysis revealed staining of atypical astrocyte nuclei as well as oligodendrocyte nuclei (Fig. 3C), a finding indicative of the presence of polyomavirus particles in the lesion and confirming the diagnosis of PML. In contrast to the positive staining in the brain lesion, the intestinal mucosa specimens obtained before the administration of natalizumab were uniformly negative.

DETECTION AND IDENTIFICATION OF JC VIRUS

To allow more specific detection of JC virus and to study the temporal relationship between the administration of natalizumab and viral replication, we analyzed the available serum samples and brain tissue for sequences of the JC virus genome. We performed a quantitative real-time polymerase-chain-reaction assay using primers specific for JC virus (PEP3 and PEP6), as described previously.[6] No viral DNA was detected in serum obtained at multiple times from April 1999 through February 2003 (Table 1) or in the fresh-frozen intestinal samples obtained at surgery in 2000 while the patient was being treated with several potentially immunosuppressive drugs. However, JC virus DNA was detected in a serum sample obtained two months before admission, while the patient was receiving monthly infusions of 300 mg of natalizumab, and had increased by a factor of 12 by the time the patient was admitted (Table 1). In addition, the paraffin-embedded tissue of the brain lesion contained a high viral load (Table 1).

To identify the JC virus genotype, we amplified a 215-bp fragment of the VP1 major capsid protein, enabling us to differentiate among seven different genotypes and multiple subtypes.[7] We sequenced the nucleotide fragments and looked for matches in the GenBank database (National Institutes of Health). JC virus genotype 2 was identified in both serum and brain tissue.

DISCUSSION

We report a fatal case of PML in a man with Crohn's disease treated with natalizumab. PML is a rare but often lethal and untreatable disorder of the central nervous system (CNS), with large white-matter lesions typically occurring in immunocompromised patients.[8,9] The pandemic of the acquired immu-

Table 1. Time Course of JC Viral Load in Serum and Brain.

Tissue	Date	No. of Samples	Treatment*	Test for JC Virus DNA†
Serum	April–November 1999	6	Infliximab, azathioprine	Negative
	April 2000	1	Budesonide, azathioprine	Negative
	March–May 2002	6	Natalizumab, azathioprine	Negative
	June 2002–January 2003	10	Azathioprine (until November 2002)	Negative
	February 2003	1		Negative
	May 2003	1	300 mg of IV natalizumab per month (total, 3 doses), beginning in March 2002	520 copies/ml
	July 2003	1		6600 copies/ml
Brain	July 2003	1	300 mg of IV natalizumab per month (total, 5 doses), beginning in February 2003	500,000 copies/cell‡

* IV denotes intravenous.
† Serum samples containing fewer than 125 copies per milliliter were considered negative.
‡ The number shown is the median number of copies of JC virus DNA in DNA extracts from four slices (range, 2.2×10^5 to 3.9×10^6).

nodeficiency syndrome has resulted in a sharp rise in deaths associated with PML, to an estimated 6.1 cases per 10 million persons in 1987,[10] but PML also occurs in patients with impaired cellular immunity from other causes. In transplant recipients, the most frequently observed symptoms of PML are hemiparesis (in 50 percent), apathy (in 46 percent), and confusion (in 38 percent).[11] The pathogenesis of PML has been associated with reactivation of JC virus, a human polyomavirus. Polyomavirus infection is widespread, and antibodies are detected in serum in 50 to 85 percent of persons in the United States and Europe.[12] After primary infection, the virus resides in the kidney,[13] and it is not entirely clear how the virus is transported to the brain. It is assumed that B cells deliver the virus to the oligodendrocytes, but active replication does not appear to occur in the blood.[14,15]

Our patient had initially received a diagnosis of an astrocytoma on the basis of the predominant frontal lesion, a high number of atypical astrocyte nuclei, and an increase in the Ki67-MIB1 proliferation index in the resected frontal lesion. However, we revisited this patient's course after Elan and Biogen Idec had publicly released two case reports of PML in patients with multiple sclerosis treated with a combination of natalizumab and interferon beta-1a.[4]

In retrospect, initially circumstantial evidence was already present to support a diagnosis of PML, such as the absence of contrast enhancement in the brain lesions, the presence of multiple lesions,[16] the presence of foamy macrophages, and the finding of ground-glass nuclear oligodendrocyte inclusions on histologic examination.[17] The diagnosis was not considered, however, because of the pathology report. Immunostaining for polyomaviral large T antigen provided strong evidence of the diagnosis of PML in this patient. Even more convincing were the findings of high levels of JC virus–specific DNA in the brain lesions and of the same JC virus genome sequences in the serum two months before the clinical onset of PML. We found the JC virus genotype 2 in serum and brain samples from our patient. JC virus genotypes 1 and 4 are predominant in Europe,[18] but genotype 2 has been associated with the development of PML.[18,19]

We identified a clear temporal relationship between the monthly natalizumab treatments and the occurrence of JC virus replication in our patient. Although he had been treated with corticosteroids and the immunomodulators infliximab (a monoclonal antibody against tumor necrosis factor) and azathioprine, JC virus DNA appeared in the serum only after the reintroduction of natalizumab as monotherapy. We do not know whether interrupting natalizumab therapy when the JC virus DNA first appeared in the serum would have prevented full-blown PML. An early analysis of cerebrospinal fluid for JC virus DNA would also have confirmed the occurrence of viral replication and is recommended when PML is clinically suspected.

Natalizumab, a humanized IgG4 antibody targeting α_4 integrins, is a member of an emerging class of drugs: the selective adhesion-molecule (SAM) inhibitors. The α_4 integrins are selectively

involved in leukocyte transport to the gut and the brain.[20] Natalizumab both blocks the engagement of $\alpha_4\beta_7$ integrin with endothelial mucosal addressin-cell adhesion molecule 1 in the gut and blocks the engagement of $\alpha_4\beta_1$ integrin with vascular-cell adhesion molecule 1, which is expressed on the endothelium of various organs, including the brain.[20] Two controlled trials suggesting the efficacy and tolerability of SAM inhibitors in patients with Crohn's disease[2,3] led to two larger multicenter trials designed to evaluate the therapeutic potential of natalizumab: ENACT-1, involving the induction of clinical remission, and ENACT-2, involving the maintenance of natalizumab-induced remission. Our patient participated in both trials.

The ability of natalizumab to inhibit leukocyte transport to the gut and the CNS selectively has been invoked to explain the limited burden of infectious complications associated with the clinical use of this compound. Moreover, because α_4 integrins are not expressed by neutrophils, blocking the function of these receptors is unlikely to compromise the immune defense against bacterial infections. Nevertheless, the findings in our patient and in the two patients with multiple sclerosis demonstrate that the use of SAM inhibitors such as natalizumab can be associated with the reactivation of latent infection with JC virus. However, we cannot exclude the possibility that the intermittent lymphopenia in our patient contributed to the reactivation of JC virus. JC virus replication could have started in the kidney or in lymphoid tissue, and natalizumab probably impaired JC virus–primed transport of CD4+ helper T cells and CD8+ cytotoxic T cells to the brain, resulting in fulminant viral replication in infected oligodendrocytes and astrocytes.

The respective roles of deficient CD4+ helper T cells and deficient CD8+ cytotoxic T cells in the reactivation of JC virus infection are still debated,[21] but the inhibition of α_4 integrins has been shown to impede the transport of both types of cells to the CNS.[22] Furthermore, $\alpha_4\beta_1$ integrin is also expressed at high levels on endothelial cells, which are an essential constituent of the blood–brain barrier.[23,24] If β_1 integrins have a crucial role in stabilizing the blood–brain barrier, the inhibition of these molecules by natalizumab may also have facilitated the infiltration of JC virus particles into the CNS.

In conclusion, our case report demonstrates that polyomavirus replication leading to PML, a life-threatening disorder, can occur in patients who receive natalizumab. Since our patient had previously received other immunomodulatory agents with no reactivation of JC virus infection, further studies are needed to establish to what extent α_4-integrin antibodies and other SAM inhibitors increase the risk of opportunistic CNS infection.

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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.

BRIEF REPORT

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis

B.K. Kleinschmidt-DeMasters, M.D., and Kenneth L. Tyler, M.D.

SUMMARY

A 46-year-old woman with relapsing–remitting multiple sclerosis died from progressive multifocal leukoencephalopathy (PML) after having received 37 doses of natalizumab (300 mg every four weeks) as part of a clinical trial of natalizumab and interferon beta-1a. PML was diagnosed on the basis of the finding of JC viral DNA in cerebrospinal fluid on polymerase-chain-reaction assay and was confirmed at autopsy. Nearly every tissue section from bilateral cerebral hemispheres contained either macroscopic or microscopic PML lesions. There was extensive tissue destruction and cavitation in the left frontoparietal area, large numbers of bizarre astrocytes, and inclusion-bearing oligodendrocytes, which were positive for JC virus DNA on in situ hybridization.

Progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the central nervous system (CNS), is associated with high rates of morbidity and mortality and occurs almost exclusively in immunocompromised patients.[1] We describe a patient with multiple sclerosis who died of PML after receiving natalizumab (Tysabri, Biogen Idec) as part of a clinical trial conducted to test the safety and efficacy of natalizumab in combination with interferon beta-1a (Avonex, Biogen Idec) in the treatment of relapsing–remitting multiple sclerosis. To our knowledge, there have been no prior reports of the concomitant association of multiple sclerosis and PML.

Natalizumab is a humanized monoclonal antibody against α_4 integrins that was recently introduced for the treatment of multiple sclerosis. The drug was withdrawn from the market after reports of the development of PML in two patients with multiple sclerosis who were receiving natalizumab and interferon beta-1a in clinical trials. An additional case of PML, in a patient receiving natalizumab for the treatment of Crohn's disease, is described elsewhere in this issue of the *Journal*.[2]

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This article was published at www.nejm.org on June 9, 2005.

N Engl J Med 2005;353:369-74.

CASE REPORT

A 41-year-old, right-handed woman began to have numbness and burning pain in her right foot and leg and tingling numbness and clumsiness in her right hand in June 1999. She had a history of migraine and transient numbness of the left hand. A neurologic examination revealed increased tone on her right side and generalized hyperreflexia (3+) with normal plantar responses. In September 1999, magnetic resonance imaging (MRI) with contrast medium showed four small, nonenhancing foci of increased signal in the

corona radiata bilaterally on the fluid-attenuated inversion recovery (FLAIR) sequences. Electromyography and nerve-conduction studies showed no abnormalities. Six weeks later, her leg symptoms had improved, but the patient reported new visual blurring in her right eye. The visual acuity of the right eye was 20/100, and that of the left was 20/15. Examination of cerebrospinal fluid in November 1999 showed 1 white cell per cubic millimeter, 55 mg of protein per deciliter, and normal values for glucose (64 mg per deciliter [3.6 mmol per liter]), IgG (3.2 mg per deciliter), the IgG index (0.57), and the IgG-synthesis rate (0.3 mg per 24 hours). No oligoclonal bands were detected in a specimen of cerebrospinal fluid that was concentrated by a factor of 80. Levels of vitamin B_{12} and folate were normal, tests for antinuclear antibodies and anticentromere antibodies were negative, and thyroid-function tests were normal. A complete blood count was also normal, except for mild leukocytosis (11,200 cells per cubic millimeter).

In January 2000, MRI showed two new nonenhancing parietal lesions with increased FLAIR signal and decreased T_1-weighted signal. In February 2000, the patient reported that her vision was normal and that her right-sided numbness had nearly resolved. She began receiving 30 μg of interferon beta-1a intramuscularly each week, tizanidine, calcium, magnesium, and vitamins B, C, and E for presumed multiple sclerosis (Table 1). In May 2000, she began taking tamsulosin for difficulty with bladder emptying and citalopram for depression.

In March 2001, the patient noted worsening vision, band-like paresthesias around her back and abdomen, and increasing weakness and spasticity of her legs. The strength of both legs was mildly decreased (4+/5), and her gait was slightly spastic, although her deep tendon reflexes were normal. She received 500 mg of methylprednisolone twice daily intravenously for five days (March 16 through 20, 2001) for a suspected exacerbation of multiple sclerosis. In September 2001, she reported some decline in fine motor skills in her hands and worsening spasticity in her legs as well as some decline in cognition, including short-term memory, and began taking donepezil. She had a score of 2.5 on the Kurtzke Expanded Disability Status Scale (EDSS) in March 2002 (range of scores, 0 to 10, with higher scores indicating a greater degree of disability).

In April 2002, the patient was enrolled in a randomized, placebo-controlled, parallel-group, multicenter study designed to determine the safety and efficacy of natalizumab combined with interferon beta-1a in patients with relapsing–remitting multiple sclerosis (the Biogen Idec and Elan 1802 SENTINEL trial). At the time of her enrollment, T_2-weighted MRI showed approximately nine lesions and her EDSS score was 0. She continued to take 30 μg of interferon beta-1a intramuscularly weekly throughout the study. Additional medications at study entry included citalopram, rofecoxib, and tramadol in combination with acetaminophen.

During the study, the patient received a total of 30 doses of natalizumab (300 mg, or approximately 6 mg per kilogram of body weight, each) by intravenous infusion at four-week intervals between April 12, 2002, and July 9, 2004. She also received tizanidine, donepezil, and briefly, galantamine. In July 2004, she was enrolled in an open-label extension study (Biogen Idec/Elan 1808) and received seven additional 300-mg doses of natalizumab at four-week intervals, with the last dose given on January 18, 2005. No antibodies developed against either interferon beta-1a or natalizumab. Pharmacokinetic studies showed that the clearance of natalizumab in the patient (0.0136 liter per hour) was similar to the median value in the study population (0.0138 liter per hour). A follow-up T_2-weighted MRI study in April 2003 showed five new or enlarging lesions. A similar study in April 2004 showed one new or enlarging lesion. No enhancing lesions were noted. Unfortunately, these MRI scans were not available for review, and the reports specified only the number of lesions, not the location. No clinical or suspected relapses of multiple sclerosis were identified, and the patient's EDSS score remained between 0 and 2 through July 2004.

In November 2004, the patient reported new problems with hand–eye coordination, including difficulty writing and typing, as well as problems with her speech. A mental-status examination performed at that time showed a decreased fund of in-

Table 1. Doses and Timing of Treatments for Multiple Sclerosis.

Treatment*	Treatment Interval
Interferon beta-1a, 30 μg IM	February 2000–January 2005
Methylprednisolone, 500 mg IV twice daily	March 16–20, 2001 December 15–19, 2004 January 5–9, 2005
Natalizumab, 300 mg IV every 4 weeks	April 12, 2002–January 18, 2005

* IM denotes intramuscularly, and IV intravenously.

formation, minor errors on a drawing of a three-dimensional cube and on tests of mathematical skills, and reduced immediate recall on a word-learning test. Her cranial nerves were normal. Her strength was intact, but she had mildly increased tone in her legs and hyperactive (3+) reflexes bilaterally. In December 2004, right-sided numbness developed and word-finding difficulty increased. The patient had difficulty carrying on a conversation and became increasingly forgetful. A neurologic examination revealed difficulty with expressive speech, with preserved comprehension, some right–left confusion, irregular saccadic eye movements, and increased tone on her right side. She received methylprednisolone (500 mg intravenously twice daily) from December 15 through 19, 2004. An MRI study performed on December 15 showed a large area of increased T_2-weighted and decreased T_1-weighted signal in the left frontal lobe posteriorly involving the subcortical white matter and extending into the centrum semiovale and corona radiata, without enhancement or mass effect (Fig. 1A). A second area of abnormal signal was noted in the right posterior parietal lobe. On December 29, 2004, a right-sided hemiparesis with an extensor plantar response was noted.

On January 5, 2005, the patient's condition was judged to be worse, with increasing right-sided hemiparesis and worsening nonfluent aphasia. Her right-arm strength was 0/5, and her right-leg strength was 2/5 proximally and 0/5 distally. On the assumption that her clinical deterioration represented an exacerbation of multiple sclerosis, she received another five-day course of methylprednisolone, beginning on January 5, 2005 (500 mg intravenously twice daily). Her last dose of natalizumab was given on January 18, 2005. On January 24, 2005, her white-cell count was 14,400 per cubic millimeter (77 percent neutrophils, 18 percent lymphocytes, 4 percent monocytes, and 1 percent eosinophils), with an absolute lymphocyte count of 2500 per cubic millimeter.

The patient's neurologic status continued to decline, and she was hospitalized on February 12, 2005. On admission, she was unresponsive, with a right-sided gaze preference. She had a marked spastic right-sided hemiplegia and some left-sided weakness. An MRI scan obtained on February 12 (Fig. 1B and 1C) showed a dramatic increase in the extent of the high T_2-weighted and low T_1-weighted signal abnormalities in the left hemisphere, with extension of the lesion to the frontal, parietal, and temporal lobes and across the corpus callosum to the right frontal lobe. New midbrain and pontine lesions were also present. There was no enhancement or mass effect. At admission, the patient had a white-cell count of 14,000 per cubic millimeter (77 percent neutrophils, 16 percent lymphocytes, 6 percent monocytes, and 1 percent eosinophils and basophils). Her absolute lymphocyte count was normal (2300 cells per cubic millimeter).

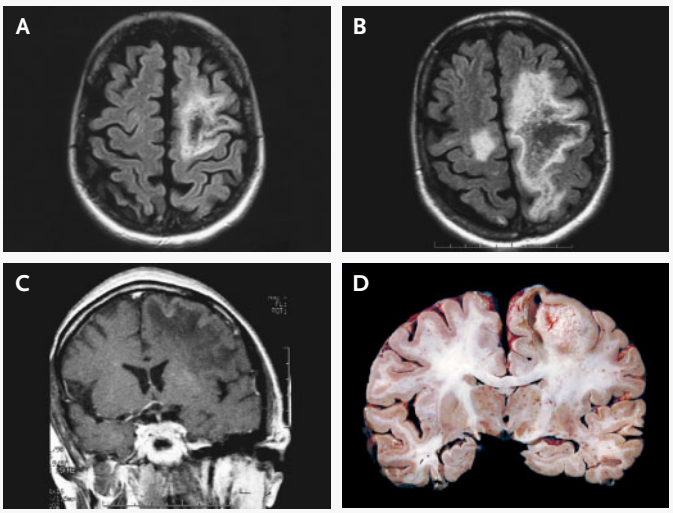

Figure 1. MRI Findings (Panels A, B, and C) and Autopsy Findings (Panel D).
In Panel A, a fast spin–echo inversion recovery sequence (repetition time, 9000 msec; echo time, 91 msec; inversion time, 2500 msec) from MRI performed on December 15, 2004, shows a large PML lesion in the left frontal lobe. In Panel B, a fast spin–echo inversion recovery sequence (repetition time, 10,002 msec; echo time, 145 msec; inversion time, 2200 msec) from MRI performed on February 12, 2005, shows an increase in the size of the previously noted lesion as well as new PML lesions in the parietal and occipital lobes in the opposite hemisphere. In Panel C, a fast spin–echo sequence (repetition time, 516 msec; echo time, 10.9 msec) from MRI performed on February 12, 2005, shows a large, low-signal PML lesion underlying the cortex in the left frontoparietal white matter. For comparison with Panel C, in Panel D, a formalin-fixed coronal section of the brain shows massive coalescent areas of cavitation of the left frontoparietal white matter, leaving only a ribbon-like strip of intact overlying cortex.

An examination of cerebrospinal fluid on February 14, 2005, revealed the following values: 53 mg of protein per deciliter, 90 mg of glucose per deciliter (5.0 mmol per liter), 4.3 mg of IgG per deciliter, an IgG index of 0.49, a ratio of IgG to albumin of 0.08, and an IgG-synthesis rate of 1.78 mg per 24 hours. No oligoclonal bands were noted. The results of Gram's staining of a cerebrospinal fluid sample were unremarkable. A polymerase-chain-reaction (PCR) assay of cerebrospinal fluid for herpes sim-

plex virus was negative, as were tests for West Nile virus IgG and IgM, eastern equine encephalomyelitis virus IgG and IgM, *Borrelia burgdorferi* IgG and IgM, and cryptococcal antigen and stains and cultures for bacteria, fungi, and acid-fast bacilli. A test for serum antibody against human immunodeficiency virus (HIV) type 1 and 2 was nonreactive. CD4+ and CD8+ T-cell counts were not assessed, but at no time was either absolute or relative lymphopenia noted.

The treating neurologist suspected PML, and a cerebrospinal fluid sample sent to the Mayo Medical Laboratories (Rochester, Minn.) for JC virus PCR testing was positive. The patient died on February 24, 2005; she was 46 years old.

METHODS AND RESULTS

Postmortem examination showed bilateral aspiration pneumonia and cachexia. There was prominent sinus histiocytosis of the lymph nodes and possible depletion of CD8+ T cells in comparison with the levels of CD4+ T cells, probably owing to severe terminal debilitation. Examination of the bone marrow showed a clinically significant leftward shift in granulocytic maturation. All other systemic organs were histologically normal; no non-CNS opportunistic infections were found. Postmortem blood samples were not tested for JC virus DNA or antibody.

The formalin-fixed, 1140-g brain was fluctuant on palpation over a large portion of the anterior left hemisphere; no discoloration or meningeal opacification was present. On coronal sectioning, this softened area corresponded to massive, coalescent areas of severe cavitation involving most of the left frontoparietal white matter, leaving only a ribbon-like strip of intact overlying cortex (Fig. 1D). Smaller, noncavitated, ovoid areas of discoloration, a typical feature of PML, studded the remaining left-hemispheric white matter, particularly at the junctions between cortical gray matter and white matter, and involved the right superior frontal gyrus (Fig. 2A). A 7-mm lesion was identified in the left cerebral peduncle (Fig. 2B and 2C). No multiple-sclerosis plaques were discernible in the corona radiata.

The brain stem, spinal cord, and optic chiasm were submitted in toto for histologic examination. Sections (total, 73 blocks) from the brain and spinal cord were stained with hematoxylin and eosin, with one fourth of the sections also stained with Luxol fast blue and periodic acid–Schiff for myelin. All sections were devoid of acute anoxic injury and vasculitis. Areas of PML showed near-total loss of myelin, an influx of macrophages, and numerous reactive astrocytes, but no perivascular or parenchymal lymphocytic inflammation (Fig. 2D). Astrocytes with bizarre, enlarged hyperchromatic nuclei, a typical finding in PML, were common, even in smaller lesions (Fig. 2D). There were large numbers of oligodendrocytes with the classic violaceous intranuclear inclusions of PML (Fig. 2E). Cells with inclusions had a strong positive signal for JC virus DNA on in situ hybridization (probe 40847, Enzo Life Sciences) (Fig. 2F).

In addition to the PML lesions seen on gross examination, myriad minute lesions were easily identified microscopically in virtually every section examined from the left cerebral hemisphere, as well as in most of the sections from the right side and all of the brain-stem sections. PML was found only focally in the cerebellum; no granule-cell depletion was seen. The optic nerve, chiasm, and spinal cord contained neither PML lesions nor multiple-sclerosis demyelinating lesions. Examination of the spinal cord showed unilateral wallerian degeneration that was due to the cavitated lesions involving the left motor strip and internal capsule. Remote cortical microinfarctions were found in the right superior frontal and parietal gyri and splenium of the corpus callosum.

DISCUSSION

PML is a demyelinating disease of the CNS caused by lytic infection of oligodendrocytes by JC polyomavirus. Primary JC virus infection occurs in childhood and is asymptomatic. JC virus antibodies are detectable in approximately 50 to 70 percent of the adult population.[3,4] After the primary infection, JC virus remains latent in kidneys and lymphoid organs. Up to 64 percent of healthy adults have shedding of JC virus in urine in the absence of any clinical symptoms, suggesting that asymptomatic active JC virus infection is common in immunocompetent persons.[5] In contrast, PML occurs almost exclusively in immunocompromised persons, particularly those with depressed cell-mediated immunity resulting from HIV infection, hematologic cancers, or immunosuppressive medications.[1] In recipients of bone marrow transplants, PML has also been associated with treatment with rituximab, an antibody against CD20 expressed on B cells,[6] and cases of PML-like CNS demyelinating illness have been reported in patients with rheumatic diseases treated

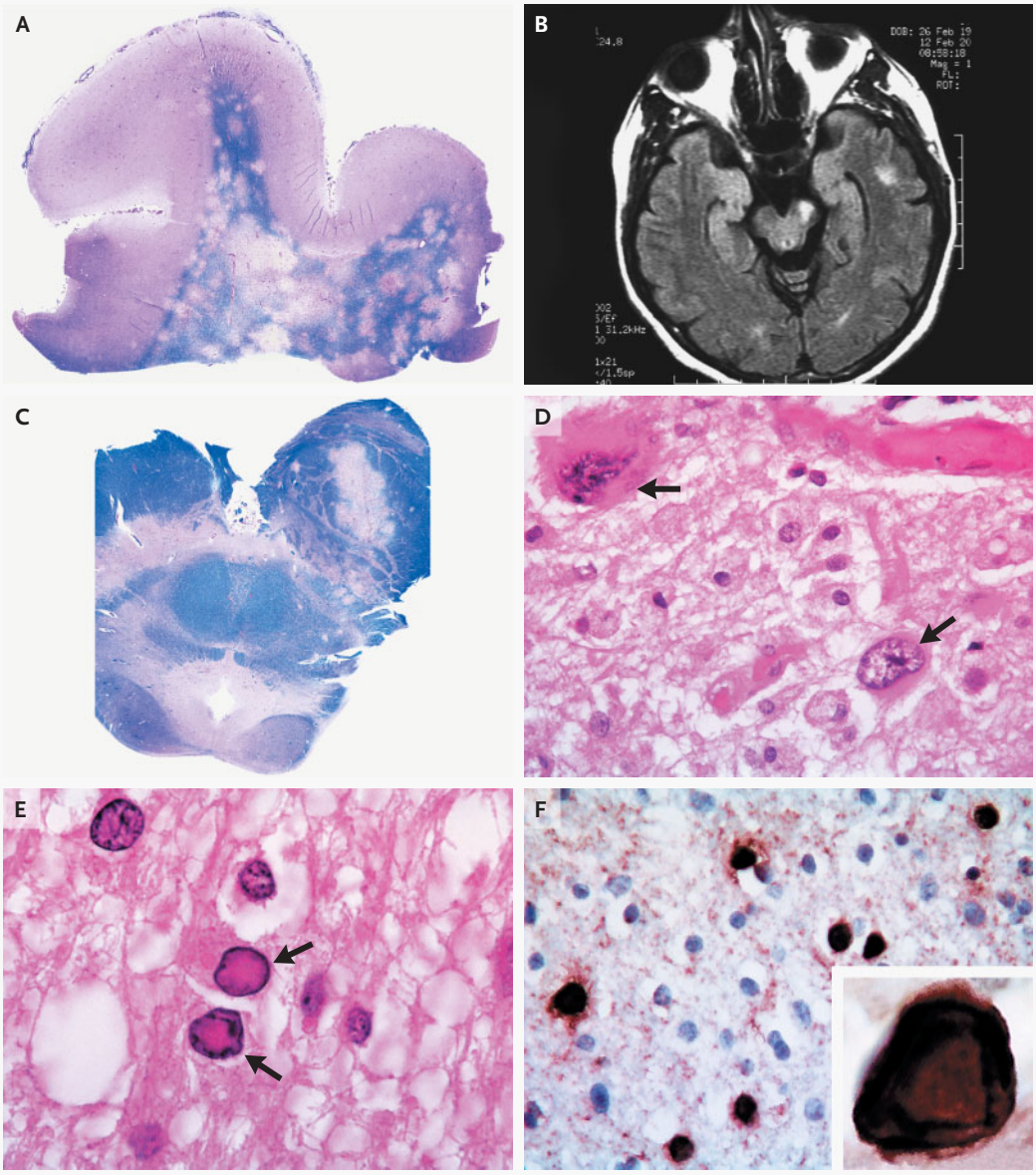

Figure 2. Histologic and MRI Findings.

Panel A shows smaller, noncavitated, ovoid areas of discoloration typical of PML studding the left-hemispheric white matter, particularly at the junctions of cortical gray matter and white matter, as well as the right superior frontal gyrus (whole-mount section stained for myelin with Luxol fast blue–periodic acid–Schiff). In Panel B, a fast spin–echo inversion recovery sequence (repetition time, 10,002 msec; echo time, 145 msec; and inversion time, 2200 msec) from MRI performed on February 12, 2005, shows PML lesions in the left cerebral peduncle of the midbrain, left temporal lobe, and both occipital lobes. For comparison with Panel B, Panel C shows a discrete PML lesion, 7 mm in diameter, in the left cerebral peduncle (whole-mount section stained for myelin with Luxol fast blue and periodic acid–Schiff). In Panel D, PML lesions are characterized by a near-total loss of myelin, an influx of macrophages, and numerous bizarre astrocytes (arrows), but no perivascular or parenchymal lymphocytic inflammation (hematoxylin and eosin). Panel E shows large numbers of oligodendrocytes with the violaceous intranuclear inclusions characteristic of PML; several infected glial cells are also present (arrows) (hematoxylin and eosin). In Panel F and the inset, cells with inclusions have a strong positive nuclear signal for JC virus (dark reddish brown) of PML on in situ hybridization (diaminobenzidine used as the chromagen with a light hematoxylin counterstain).

with antagonists of tumor necrosis factor α.[7] Although multiple sclerosis is an immune-mediated disorder, to our knowledge, patients with multiple sclerosis have not previously been identified as at increased risk for PML.

Natalizumab is a humanized monoclonal antibody against α_4 integrins that was approved by the Food and Drug Administration for the treatment of several immune-mediated disorders, including multiple sclerosis and inflammatory bowel disease.[8-10] Antibodies against α_4 integrins inhibit the binding of cells expressing $\alpha_4\beta_1$ integrin and $\alpha_4\beta_7$ integrin (e.g., lymphocytes) to vascular-cell adhesion molecule 1 and mucosal addressin-cell adhesion molecule 1 on endothelial cells, a critical step in the diapedesis of lymphocytes across blood vessels into the CNS and mucosal organs.[10,11] Treatment with antibodies against α_4 integrins prevents inflammatory cells from crossing the blood–brain barrier and inhibits the accumulation of immune cells in the CNS in animals with experimental allergic encephalomyelitis.[11-13]

Our patient received interferon beta-1a for nearly five years and received combined therapy with natalizumab and interferon beta-1a for just over two years as part of the SENTINEL trial. We therefore cannot rule out a potential contributory role of interferon beta-1a in the genesis of this patient's PML. However, to date, there have been no reported cases of PML in patients receiving interferon beta-1a monotherapy.

The diagnosis of PML was established on the basis of a positive PCR assay for JC viral DNA in cerebrospinal fluid in a patient with clinical and neuroimaging findings that were typical of PML, and the diagnosis was confirmed at autopsy. The severity and extent of disease were dramatic. Nearly every tissue section from bilateral cerebral hemispheres that we examined had either macroscopic or microscopic PML lesions, ranging from minute to massive in size. There was extensive tissue destruction and cavitation in the left frontoparietal area, and the lesions contained large numbers of oligodendrocytes with inclusions. No inflammatory response was present. Although no formal quantitation was performed, the extent of the PML involvement was similar to or exceeded that seen in HIV-infected patients before the advent of highly active antiretroviral therapy.

Dr. Tyler is supported by the Reuler–Lewin Family Professorship of Neurology.

We are indebted to the neurologist who cared for the patient; to Dr. Kate Dawson from Biogen Idec, for furnishing some additional clinical and laboratory information on the patient; to Ms. Lisa Litzenberger for her photographic expertise; to the histologic technicians, supervised by Mr. David Davis, for slide preparation; and to Ms. Cindy McNair for assistance in the preparation of the manuscript.

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BRIEF REPORT

Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab

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SUMMARY

We describe the clinical course of a patient with multiple sclerosis in whom progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the central nervous system, developed during treatment with interferon beta-1a and a selective adhesion-molecule blocker, natalizumab. The first PML lesion apparent on magnetic resonance imaging was indistinguishable from a multiple sclerosis lesion. Despite treatment with corticosteroids, cidofovir, and intravenous immune globulin, PML progressed rapidly, rendering the patient quadriparetic, globally aphasic, and minimally responsive. Three months after natalizumab therapy was discontinued, changes consistent with an immune-reconstitution inflammatory syndrome developed. The patient was treated with systemic cytarabine, and two months later, his condition had improved.

Progressive multifocal leukoencephalopathy (PML) is a rare, oligodendroglial infection caused by the polyomavirus JC virus. It usually occurs in people infected with the human immunodeficiency virus (HIV), but it has also been reported in immunocompromised patients receiving prolonged treatment with methotrexate, cyclophosphamide, and azathioprine. PML has not been reported in persons with multiple sclerosis, despite the frequent use of these medications to treat the disease.

We describe the clinical course of a patient with multiple sclerosis in whom PML developed during treatment with interferon beta-1a (Avonex, Biogen Idec) and natalizumab (Tysabri, Biogen Idec and Elan), a monoclonal antibody against α_4 integrins. Despite the discontinuation of these medications, his PML progressed rapidly. An immune-reconstitution inflammatory syndrome developed three months after the cessation of natalizumab therapy, and the patient became bedridden and minimally responsive. Treatment with intravenous cytarabine was begun, and shortly thereafter, his condition improved. The reasons for his clinical deterioration and recovery are not clear.

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This article was published at www.nejm.org on June 9, 2005.

N Engl J Med 2005;353:375-81.

CASE REPORT

In 1983, a 23-year-old right-handed man had a month-long episode of right hemianesthesia, his first symptom of what proved to be relapsing–remitting multiple sclerosis. He had a second attack in 1989 and had two or three attacks per year between 1989 and 1998. His medical history was also notable for the Ramsay Hunt syndrome with auricular zoster in 1998, a malignant melanoma excised from his back with negative margins in 1996, and a cleft lip and palate. A sister also had relapsing–remitting multiple sclerosis.

He started receiving weekly intramuscular injections of interferon beta-1a in 1998 (Fig. 1). The frequency of relapses decreased to one per year until 2001. From 2001 through 2002 he had three exacerbations, prompting his enrollment in a double-blind, randomized, placebo-controlled trial of 300 mg of natalizumab every four weeks plus interferon beta-1a as compared with a placebo infusion plus interferon beta-1a. At entry into the study in October 2002, he had an old left afferent pupillary deficit, mild right lateral rectus palsy, right-sided lower-motor-neuron facial paresis, mild ataxia, a score on the Kurtzke Expanded Disability Status Scale of 2 (scores can range from 0 to 10, with higher scores indicating more severe disease), and evidence of focal, nonenhancing white-matter lesions on T_2-weighted magnetic resonance imaging (MRI) characteristic of multiple sclerosis. During the next two years he had no further relapses. T_2-weighted MRI of the brain, performed as part of the study protocol in October 2003, showed multiple small, nonenhancing periventricular and subcortical hyperintensities consistent with the presence of multiple sclerosis. But in October 2004, in addition to a small, new, enhancing periventricular lesion typical of multiple sclerosis (not shown), a new nonenhancing lesion of the right frontal lobe appeared on another MRI scan obtained as part of the protocol (Fig. 2A).

In November 2004, the patient's physician observed uncharacteristic, inappropriate behavior during a routine study visit. In mid-December, the patient told his family and friends that he was having difficulty with attention and concentration. Progressive left hemiparesis, dysarthria, and cognitive impairment subsequently developed. MRI of the brain showed new, extensive abnormalities, including a large hyperintense lesion of the right frontal lobe, bilateral subinsular white-matter lesions that spared the cortex, and scattered lesions in the white matter, deep gray matter, and brain stem, with a few punctate foci of enhancement consistent with the presence of noninflammatory PML[1] (Fig. 2B). After receiving 28 infusions, the last in mid-December 2004, the patient stopped taking the study drug, which was revealed to be natalizumab.

The patient was not classically immunocompromised at clinical presentation: he had no known risk factors for HIV infection, serologic analysis for HIV was twice negative, and the total leukocyte count (8.6×10^3 per cubic millimeter) and values for lymphocyte subgroups were normal (CD4:CD8 ratio, 1.1; CD4 T-cell count, 637 per cubic millimeter; and CD8 T-cell count, 564 per cubic millimeter). Analysis of cerebrospinal fluid in early February showed no white cells and 88 red cells per cubic millimeter, normal cytologic findings, and normal concentrations of both total protein (41 mg per deciliter) and glucose (62 mg per deciliter [3.4 mmol per liter]). The IgG index (a measure of the IgG production in the cerebrospinal fluid) was elevated (0.7), and two oligoclonal bands were seen. JC virus DNA was detected by the polymerase chain reaction (PCR)[2] in the serum (2500 copies per milliliter), peripheral-blood mononuclear cells (225 copies per milliliter), and cerebrospinal fluid (6050 copies per milliliter). Biopsy of the right frontal lobe showed abundant areas of astrogliosis and microgliosis in the deep layers of cortical gray matter, with underlying white matter showing demyelination, dense infiltration of macrophages, and sparse lymphocytes. Scattered enlarged oligodendrocytes contained intranuclear inclusions positive for papovavirus (Fig. 3). In situ hybridization showed JC virus but no evidence of herpes simplex virus or cytomegalovirus. A workup for cancer, including computed tomography (CT) of the chest, abdomen, and pelvis and whole-body positron-emission tomography, showed no masses and no areas of increased metabolism. Positron-emission tomography did show decreased cortical uptake of fludeoxyglucose F 18 within the right frontal lobe, a finding consistent with necrosis.

During the next three weeks, left hemiplegia, left-sided neglect, left hemianesthesia, apraxia of the right arm, and nonfluent aphasia developed and dysarthria worsened despite intravenous treatment with high-dose methylprednisolone. Intravenous treatment with cidofovir (5 mg per kilogram of body weight every two weeks) was initiated.

Eight days later, global aphasia, incontinence, stooped posture, and truncal instability developed. Repeated analysis of cerebrospinal fluid showed a mild pleocytosis and hemorrhage: an elevated protein concentration (58 mg per deciliter), 2 white cells and 324 red cells in the second tube obtained, and 6 white cells (30 percent neutrophils, 55 percent lymphocytes, 4 percent reactive lymphocytes, and 11 percent monocytoid cells) and 913 red cells in the subsequent tube. JC virus DNA was undetectable in peripheral-blood mononuclear cells and plasma but remained present in the cerebrospinal

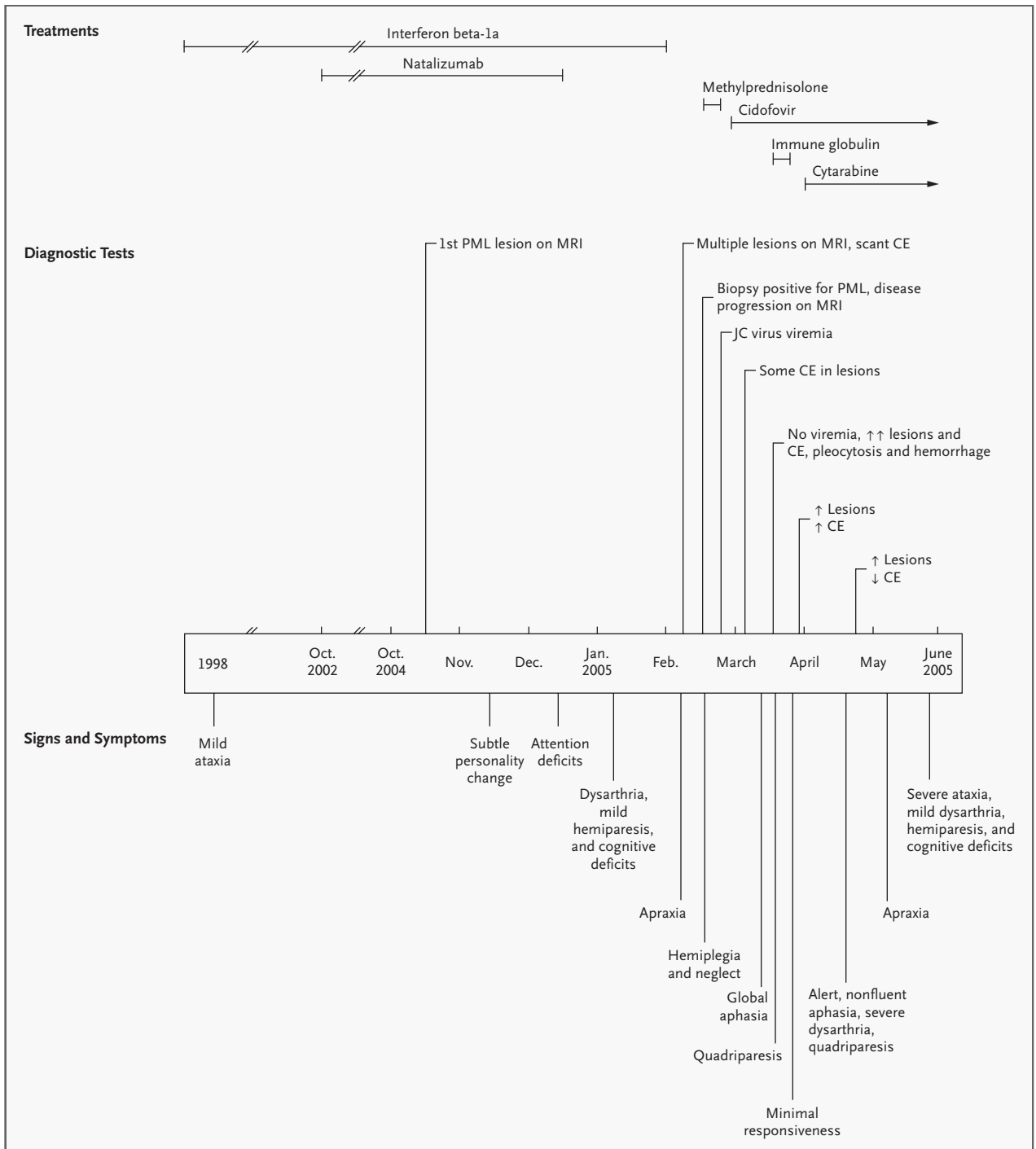

Figure 1. Summary of the Patient's Clinical Course, Treatments, and Results of Laboratory Tests.

CE denotes contrast enhancement. One upward-pointing arrow indicates a moderate increase, two upward-pointing arrows a substantial increase, and one downward-pointing arrow a moderate decrease.

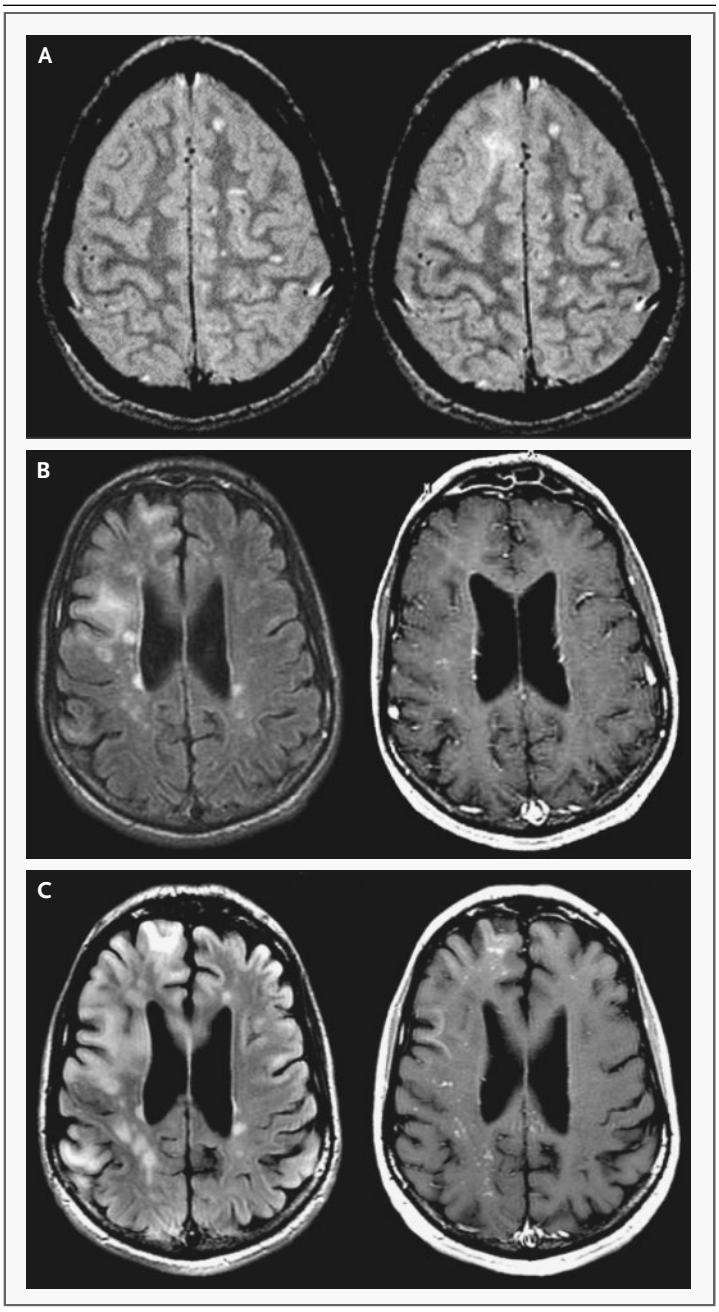

Figure 2. Progression of Abnormalities on MRI.

Panel A shows images obtained before the development of PML-related symptoms. An axial T_2-weighted MRI obtained in October 2003 (left-hand side) shows multiple small focal lesions in the white matter consistent with the presence of multiple sclerosis. In October 2004 (right-hand side), a large, new, ill-defined lesion is seen in the right frontal lobe, which will later prove to be PML. In early February 2005 (Panel B), axial fluid-attenuated inversion recovery MRI (left-hand side) shows more extensive disease in the right frontal white matter, with cortical sparing and several scattered lesions. After the addition of intravenous contrast medium (right-hand side), a few small foci of enhancement are apparent in the right hemisphere. In late March 2005 (Panel C), axial fluid-attenuated inversion recovery MRI (left-hand side) shows dramatic progression, especially in the right hemisphere, with lesions now extending into the anterior corpus callosum. After the addition of intravenous contrast medium (right-hand side), there is a substantial increase in the foci of enhancement.

fluid (2245 copies per milliliter). PCR of cerebrospinal fluid for herpes simplex virus, human herpesvirus 6, varicella–zoster virus, Epstein–Barr virus, and enteroviruses was negative, as were the results of Gram's staining, bacterial culture, cryptococcal staining, staining for acid-fast bacilli, and serologic analysis for Lyme disease. CT of the head showed no evidence of hemorrhage. MRI of the brain five weeks later (Fig. 2C) showed marked progression of the white- and gray-matter lesions and extensive foci of enhancement, particularly in the right hemisphere, findings consistent with inflammation.

The patient's hospital course was further complicated by methicillin-resistant *Staphylococcus aureus* bacteremia, urosepsis, upper gastrointestinal bleeding, elevated concentrations of serum aminotransferases, transient hyponatremia, and transient lymphopenia. The nadir absolute lymphocyte count was 647 cells per cubic millimeter, with 188 CD4+ T cells per cubic millimeter, 214 CD8+ T cells per cubic millimeter, and a CD4:CD8 ratio of 0.9.

His condition continued to deteriorate, despite the administration of three infusions of cidofovir over a period of eight weeks and a five-day course of intravenous immune globulin (2 g per kilogram per day). Left hemiplegia, anesthesia, and neglect were now accompanied by right hemiparesis and apraxia, nonfluent aphasia, severe cognitive impairment, and a fluctuating level of alertness, rendering the patient bedridden, mute, and almost completely noncommunicative. Electroencephalography at this time showed diffuse slowing and bilateral periodic epileptiform discharges that did not respond to treatment with intravenous benzodiazepam.

His treating physicians began intravenous treatment with cytarabine (2 mg per kilogram per day for five days) in early April. This caused pancytopenia, requiring the administration of erythropoietin and granulocyte colony-stimulating factor, and fever; the latter resolved within 12 hours after empirical antibiotic treatment.

Unexpectedly, the patient began talking two weeks after the initiation of cytarabine therapy. At the time of the most recent follow-up assessment, he continued to show neurologic improvement. After one month of cytarabine therapy, his right-sided weakness and left-sided sensory loss resolved, and his left hemiplegia, neglect, aphasia, and dysarthria began to improve. He still had severe deficits, including dysarthria, spastic left hemiparesis, cognitive impairment, and parkinsonism. He required the assistance of two persons to move from a bed to a chair. MRI of the brain obtained three weeks after treatment with cytarabine was begun showed further progression of disease in the left cerebellar white matter, right external and internal capsule, and frontal lobes bilaterally. The only detectable improvement was a slight decrease in the amount of contrast enhancement.

A second course of cytarabine was given four weeks after the first, without any complications. By the end of May 2005, the patient was starting to walk and was having meaningful conversations regarding the reasons for his clinical deterioration. He still had disabling ataxia, cognitive impairment, mild neglect, and mild left hemiparesis.

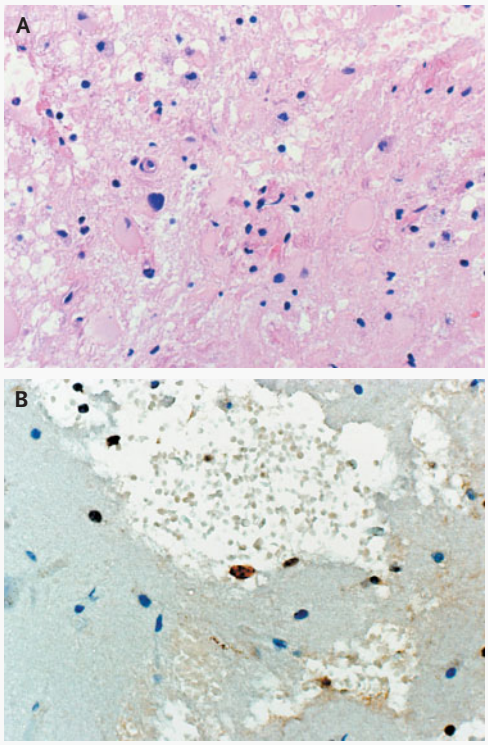

Figure 3. Brain-Biopsy Specimen.
Panel A shows a focus of demyelination (hematoxylin and eosin), and Panel B immunohistochemical staining for papovavirus.

DISCUSSION

Our patient is one of three patients in whom rapidly progressive PML has been shown to develop during clinical trials of natalizumab, a selective adhesion-molecule blocker, to treat relapsing–remitting multiple sclerosis or Crohn's disease.[3-5] Elsewhere in this issue of the *Journal*, Kleinschmidt-DeMasters and Tyler describe a second patient with multiple sclerosis who received combination treatment with natalizumab and interferon beta-1a[3] and Van Assche et al. describe a patient with Crohn's disease who received natalizumab alone.[4]

Our patient's condition worsened after the cessation of natalizumab therapy despite treatment with cidofovir, corticosteroids, and intravenous immune globulin, but his condition improved after the institution of systemic cytarabine therapy. His brain biopsy showed typical noninflammatory PML; however, three months after the cessation of natalizumab, what we believe to be an immune-reconstitution inflammatory syndrome developed that was characterized by widespread inflammation of the central nervous system, as shown by extensive enhancement on MRI and microscopic hemorrhages. Other remarkable features of the case include JC virus viremia and MRI evidence of PML one month before symptoms developed.

JC virus is a ubiquitous infection acquired in childhood that remains dormant in bone marrow, kidney epithelia, and spleen. Antibodies against JC virus are detectable in at least 80 percent of adults.[6] However, humoral immunity is insufficient to prevent the spread of the virus to the central nervous system. Intermittent reactivation, with shedding of live virus in the urine, has been well documented in cross-sectional studies of healthy adults and pregnant women, but this phenomenon is poorly understood. Spread of the virus to the central nervous system and the subsequent development of PML occur in immunocompromised persons — most commonly those infected with HIV, but also in some patients with lymphoma, sarcoidosis, and medication-induced immunosuppression. JC virus can enter the central nervous system directly during periods of viremia, such as those occurring during prolonged immunosuppression. Eighty

to 90 percent of patients with PML but not HIV infection die within one year.[7]

Natalizumab is highly effective at preventing recurrent inflammation in patients with multiple sclerosis.[8] Natalizumab binds to and blocks the function of α_4 integrins, adhesion molecules that promote the migration of lymphocytes into various organs, including the brain[9] and kidneys.[10] In patients with multiple sclerosis, natalizumab's most striking effect is the reduction of both contrast-enhancing lesions on MRI and clinical relapses.[8]

How natalizumab therapy alone or in combination with other immune-altering therapies could lead to JC virus viremia and PML is unknown. We speculate that the reactivation of the virus cannot be suppressed until the effects of natalizumab wear off. In our patient, JC virus viremia ended three months after treatment with natalizumab was stopped, and the biologic effects of natalizumab have been shown to wear off after about three months.[11]

Three months after natalizumab therapy was stopped, an inflammatory reaction developed in our patient's brain. In HIV-infected patients, as in our patient, inflammatory reactions against PML are a manifestation of the immune-reconstitution inflammatory syndrome and are associated with clinical deterioration and increases in the size of high signal lesions on T_2-weighted MRI but more favorable outcomes than in noninflammatory PML.[12,13] However, patients can die during the course of the immune-reconstitution inflammatory syndrome,[13] as our patient almost did, and how best to manage the JC virus infection and this inflammatory phase of PML is unknown.

Cidofovir, an antiviral agent, has been used with anecdotal success in the treatment of HIV-associated PML.[14,15] However, in vitro, cidofovir fails to kill glial cells infected with JC virus,[16] and there are no controlled studies to support its use. After three courses of cidofovir, our patient's condition continued to deteriorate.

Cytarabine kills JC virus in vitro.[16] This observation led to a randomized, controlled trial of the drug in HIV-infected patients with PML, which failed to show efficacy.[17] However, the penetration of cytarabine into the central nervous system is poor, and only one patient in this trial had contrast enhancement on MRI.[18] We chose to administer cytarabine to our patient, given the failure of cidofovir and the lack of other options, and subsequently, his condition improved. The reasons for this improvement are not clear. It is possible that the extensive breakdown of his blood–brain barrier improved penetration of cytarabine into the central nervous system, aiding in the clearance of the virus, or that its strong myelosuppressive properties curbed the inflammatory response. Alternatively, the improvement may have been due solely to clearance of the virus by the patient's reconstituted immune system.

In our patient, the first PML lesion — a frontal-lobe lesion that was indistinguishable from a multiple sclerosis lesion — was visible on neuroimaging studies two months before obvious neurologic deficits developed. Although this may be due to the relatively subtle deficits that would be expected as a result of a lesion in this area, it suggests that more frequent MRI monitoring of patients who receive natalizumab may be warranted. The appearance of lesions, particularly in or abutting the gray matter, should increase clinical suspicion of PML. Monitoring for JC virus viremia may also be useful in such patients. Our case report suggests that some degree of recovery from natalizumab-associated PML is possible.

Supported by a grant (NS43207-03) from the National Institute of Neurological Diseases and Stroke and a Wadsworth Foundation Young Investigators Award (both to Dr. Langer-Gould).

Dr. Langer-Gould reports having received consulting and lecture fees from Biogen Idec; and Dr. Pelletier, consulting fees, lecture fees, and grant support from Biogen Idec.

We are indebted to Kristin Cobb and Michael K. Gould for helpful reviews of the manuscript, to Caroline Ryschkewitsch and Eugene Major for determining the JC virus titers to Mary Owen, Heather Hinds, Keith K. Abe, and Jeffrey H. Gertsch for their outstanding clinical care of the patient, and to the patient and his family for allowing us to report his story.

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SPECIAL ARTICLE

Children in the United States with Discontinuous Health Insurance Coverage

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ABSTRACT

BACKGROUND

Estimates of the number of uninsured people in the United States usually exclude those with discontinuous coverage. The effects of gaps in insurance coverage for children on access to and use of ambulatory care are poorly understood.

METHODS

We analyzed a sample of 26,955 children under 18 years of age from the 2000 and 2001 National Health Interview Surveys. Children with discontinuous health insurance coverage were compared with those who were uninsured all year and with those who had public or private full-year coverage.

RESULTS

During the last 12 months before they were interviewed, 6.6 percent of children in the United States had no insurance and an additional 7.7 percent had gaps in insurance. Children who had full-year insurance coverage (private or public) had low rates of unmet health care needs and good access to care (delayed care, unmet medical care, and unfilled prescriptions were reported in <3 percent, and <5 percent had no usual place of care). Access to care was much worse for children who were uninsured for part of the year and for those who were uninsured for the full year (delayed care, 20.2 percent and 15.9 percent, respectively; unmet medical care, 13.4 percent and 12.6 percent, respectively; unfilled prescriptions, 9.9 percent and 10.0 percent, respectively; $P<0.01$ for all comparisons with children with full-year, private insurance coverage). In multivariate analyses adjusting for age, income, race or ethnic group, region, citizenship, family structure, parental employment, and health status, the differences in access to care persisted. As compared with the parents of children with full-year, private insurance, parents of children uninsured for the full year were far more likely to report delaying care (adjusted odds ratio, 12.65; 95 percent confidence interval, 9.45 to 16.94), as were parents of children uninsured for part of the year (adjusted odds ratio, 13.65; 95 percent confidence interval, 10.41 to 17.90).

CONCLUSIONS

Children with gaps in health insurance coverage commonly do not seek medical care, including preventive visits, and do not get prescriptions filled. These findings are important for both research and policy and point to the need for more encompassing and sensitive measures of the situation of being uninsured.

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N Engl J Med 2005;353:382-91.

IT HAS BEEN ESTIMATED THAT MORE THAN 40 million persons in the United States are uninsured,[1,2] but this often-cited number presents a narrow and misleading snapshot of insurance problems. By counting only those without coverage at a single point in time, we exclude many of the "hidden uninsured" — adults and children with discontinuous coverage — from the debates about health insurance reforms.

The precise number of people in the United States with gaps in insurance coverage is little studied and difficult to discern.[3-5] Indeed, most research about health services during the past 20 years has treated health insurance as a simple dichotomy — a person is either insured or uninsured. The limited evidence available suggests that many persons in the United States have discontinuities in coverage over time.[6] An important issue for both research and policy is the way we should view persons with insurance discontinuities: Are they more like those who are fully insured or those who are fully uninsured?

We have focused on the extent of the discontinuity of health insurance coverage for children and its effect on access to and the use of ambulatory health care, defined as well-child visits (general checkups when the child is not sick or injured) and visits to doctors' offices. Few studies have examined these issues, especially among children.[6-9] Moreover, the literature often focuses on selected subpopulations of children or involves data that do not fully reflect recent changes in the health care system or the full implementation of the State Children's Health Insurance Program.

We fill this gap with a new analysis that makes use of nationally representative data from the combined 2000 and 2001 National Health Interview Surveys, and we assess the following three aspects of access to health care: unaddressed health care needs due to cost, the existence of usual places for care, and ambulatory visits. Combining the data from two years provides a larger sample of children than the samples used in previous studies. In addition to permitting an analysis of the prevalence and effects of discontinuity of coverage, the National Health Interview Survey provides information needed to compare all children in the United States who are uninsured for part of the year with those who are uninsured for a full year and with those with public or private, full-year coverage. Our primary research questions are as follows. What characteristics do children with intermittent insurance coverage have in terms of age, family income, race or ethnic group, region of residence, citizenship, family structure, parental employment, and health status that distinguish them from other children? How does access to ambulatory care vary among children who have insurance, children who have discontinuous insurance, and children who have no insurance at all?

METHODS

CHARACTERISTICS OF THE SURVEY COMPONENTS

We used the publicly available data from the 2000 and 2001 National Health Interview Surveys to conduct this study. The National Health Interview Survey is a collection of information about the demographic characteristics, health status, and health care usage of the U.S. civilian noninstitutionalized population. The basic survey has three components — the family component includes questions administered to all family members, and the sample-adult and sample-child components include more in-depth questions administered for one adult and one child selected randomly in each family. All 26,955 unweighted cases included in the sample-child component, representing 72.3 million children under 18 years of age in 2000 and 72.6 million in 2001, are included in this study. A knowledgeable adult, typically a parent, answered questions for children under 17 years of age; 17-year-olds answered for themselves. The response rates of the 2000 and 2001 sample-child components were 79.4 percent and 80.6 percent, respectively.[10,11]

OUTCOME VARIABLES

We examined outcomes in the following areas: health care needs left unaddressed because of cost (delayed care, unmet medical care, and unfilled prescriptions), the existence of usual places for care, and ambulatory visits. Respondents were asked to consider activities during the past 12 months. Information about delayed care and unmet medical care was based on data from the family component of the survey. Other variables were constructed with data from the sample-child component. The existence of usual places for care was assessed according to whether respondents reported regular places where they sought sick care, preventive care, or both for their children.

The primary predictor variable was the child's health insurance coverage during the past 12 months. We determined the categories of insur-

ance coverage on the basis of whether the child had health insurance coverage at the time of the interview, the type of current coverage (Medicaid, State Children's Health Insurance Program, or employer-based or other private health insurance), and follow-up questions that depended on current insurance status.

If the child was currently covered, the respondent was asked whether the child had been uninsured at any time during the past 12 months. If the child was not currently covered, the respondent was asked how many months it had been since the child was last insured. On the basis of the responses, we constructed a variable encompassing the following four categories of insurance coverage: full-year uninsured (children with no coverage when interviewed and no coverage for at least 12 months before the interview); full-year insured, currently with public coverage (children with Medicaid or State Children's Health Insurance Program coverage when interviewed and no time without health insurance coverage during the past 12 months); full-year insured, currently with private coverage (children with employment-based or other private coverage when interviewed and no time without coverage during the past 12 months); and part-year uninsured (all children not falling into the other three categories).

Other predictor variables included the age of the child, family income, the child's race or ethnic group, geographic region of residence, the citizenship of the child, family structure, parental employment, and the health status of the child (i.e., global health status and activity limitations due to chronic conditions). Details of the survey and wording regarding race or ethnic group and all variables can be found at the Web site of the data-collection agency.[12]

DATA ANALYSIS

To derive estimates that represent the U.S. civilian, noninstitutionalized population, each record in the combined 2000 and 2001 National Health Interview Surveys was weighted according to person-level weights provided by the data-collection agency. We adjusted estimates for nonresponses and statistically weighted the results to reflect national population totals. Bivariate analyses were used to show the distribution of children in the four insurance groups according to age, family income, race or ethnic group, region of residence, citizenship, family structure, parental employment, and health status. Bivariate analyses were also used to show the relationship between health insurance status and unaddressed health needs, the existence of usual places for care, and ambulatory visits.

We conducted multiple logistic-regression analyses to assess the effects of health insurance coverage after adjustment for age, family income, race or ethnic group, citizenship, region of residence, family structure, parental employment, and health status. These variables were selected on the basis of the conceptual model of Aday and Andersen for predicting access to care.[13] Our use of that model incorporates age, race or ethnic group, region of residence, citizenship, family structure, and parental employment as predisposing variables; insurance status and family income as enabling variables; and health status as a need variable.

Data for the National Health Interview Survey were collected through a complex sample design incorporating stratification, clustering, and multistage sampling.[14] Estimates, standard errors of bivariate statistics, P values of statistical significance testing, odds ratios, and 95 percent confidence intervals of estimated odds ratios for the logistic model were calculated with the use of SUDAAN software, which takes into account the complex sample design of the survey.[15]

RESULTS

RATES OF INSURANCE COVERAGE

On average, in 2000 and 2001 6.6 percent of children in the United States 17 years of age and under were reported to have had no health insurance coverage during the most recent 12-month period. When children with no insurance for part of the year were included, the proportion of uninsured children more than doubled, to an average of 14.3 percent each year for 2000 and 2001 (Table 1). The majority of children (66.8 percent) were covered for the entire most recent 12-month period and had private insurance coverage at the time of the interview for the survey; 18.9 percent were covered for the entire 12 months and had public insurance coverage at the time of the interview.

CHARACTERISTICS ACCORDING TO INSURANCE COVERAGE

Table 2 compares characteristics among children in the following four insurance groups: full-year uninsured, part-year uninsured, full-year insured with public coverage, and full-year insured with

private coverage. There was considerable variation across the insurance categories. The group that was fully insured with public coverage had the highest percentage of children in low-income families (families with incomes <200 percent of the federal poverty level, at 85.1 percent, followed by full-year uninsured children, at 74.6 percent, and part-year uninsured children, at 60.6 percent). Relatively few children (18.1 percent) who are fully insured with private coverage live in low-income households. Hispanic children account for almost half (46.4 percent) of the full-year-uninsured group but only 21.8 percent of the part-year-uninsured group (P<0.01). In contrast, non-Hispanic white children account for the majority (57.5 percent) of those uninsured for part of the year and only 36.9 percent of those uninsured for the full year (P<0.01).

Geographically, relatively few children from the Northeast were in either uninsured category, and relatively more children from the South were in these groups. Children uninsured for the full year were much more likely not to be U.S. citizens (20.8 percent, vs. <5 percent for each other insurance group; P<0.01). Children uninsured for the full year and those uninsured for part of the year were very similar in terms of parental employment. On the two measures of health status, the greatest percentage of problems was reported for children with full-year public coverage; for example, 12.3 percent of these children were reported to have activity limitations. Children who were uninsured for part of the year had more health problems than children uninsured for the full year. For example, 8.3 percent of those uninsured for part of the year had activity limitations, as compared with 4.9 percent of those uninsured for the full year (P<0.05).

Table 1. Health Insurance Coverage for Children in the United States under 18 Years of Age.

Coverage during the 12 Months before the Interview	Estimated Population*		Unweighted Count†
	no. (thousands)	%	
Full-year uninsured	4680±304	6.6±0.2	2,152
Part-year uninsured	5450±323	7.7±0.2	2,138
Full-year insured			
Public coverage	13,419±637	18.9±0.4	5,298
Private coverage	47,310±1153	66.8±0.5	16,724
Total	70,859	100.0	26,312

* The total does not include an estimated 1.6 million children whose health insurance coverage during the 12 months before the interview could not be ascertained. Data were obtained from the National Health Interview Surveys, 2000 and 2001.[10,11] Plus–minus values are means ±SE.
† Unweighted counts represent the actual numbers of persons included in the survey sample.

INSURANCE COVERAGE AND UNMET NEEDS, USUAL PLACES FOR CARE, AND AMBULATORY VISITS

Bivariate Analyses

Parents of children who were fully insured with either private or public insurance reported very low rates of unaddressed health needs. In contrast, children who had part of a year or a full year without insurance were reported to have much higher rates of unaddressed health needs. For example, in the last 12 months before they were interviewed for the National Health Interview Surveys, parents of children in each fully insured group reported delayed care in less than 2.5 percent of children, as compared with 15.9 percent of children who were uninsured for the full year and 20.2 percent of those uninsured for part of the year (P<0.01). Similar patterns were found for unmet medical care and unfilled prescriptions (Table 3).

On measures related to the existence of usual places for care and ambulatory visits, the problems for children without insurance for part of the year fell between those uninsured for the full year and those insured for the full year. For example, 38.0 percent of children uninsured for the full year had no regular places for sick and preventive care, as compared with 15.0 percent of children uninsured for part of the year (P<0.01). Significantly fewer (<4.5 percent) of those with public or private full-year coverage had this lack of continuity. As compared with either group of children who were insured for the full year, about a quarter of whom had no well-child visits, children without insurance all year were more likely to have had no well-child visits (58.7 percent, P<0.01), as were children who were uninsured for part of the year (37.2 percent, P<0.01).

Adjusted Analyses

In multiple logistic-regression analyses, the status of insurance coverage had a significant effect across all measures of unaddressed health needs, the existence of usual places for care, and ambulatory visits (Tables 4 and 5). Independent of age, family income, race or ethnic group, region of residence, citizenship, family structure, parental employment, and health status, being uninsured substantially increased the likelihood that children

Table 2. Characteristics of Children According to Health Insurance Coverage.*

Characteristic	Full-Year Uninsured	Part-Year Uninsured	Full-Year Insured, Public Coverage	Full-Year Insured, Private Coverage	All Children
			percent		
Age					
0 to 5 yr	27.4±1.3†	35.0±1.2†	41.2±0.9‡	31.0±0.5	33.0±0.4
6 to 11 yr	34.4±1.4	35.3±1.3	33.1±0.9	34.2±0.5	34.1±0.4
12 to 17 yr	38.2±1.3	29.7±1.1	25.8±0.9‡	34.8±0.5	32.9±0.4
Family income under 200% of the federal poverty level	74.6±1.5‡	60.6±1.3‡	85.1±0.7‡	18.1±0.5	37.3±0.5
Race or ethnic group§					
Hispanic	46.4±1.7‡	21.8±1.1‡	25.4±0.9‡	10.4±0.3	16.5±0.4
Non-Hispanic black	12.3±1.2	17.3±1.0‡	29.2±1.1‡	10.9±0.4	14.9±0.4
Non-Hispanic other	4.4±0.7	3.4±0.5†	5.0±0.5	4.8±0.2	4.7±0.2
Non-Hispanic white	36.9±1.6‡	57.5±1.5‡	40.4±1.2‡	74.0±0.5	63.9±0.5
Region					
West	31.5±1.5‡	23.3±1.4	22.2±1.0	20.5±0.5	21.8±0.5
Midwest	13.1±1.2‡	22.7±1.2†	20.7±1.0‡	26.4±0.6	24.2±0.5
South	47.4±1.6‡	41.0±1.4‡	38.8±1.1‡	32.6±0.6	35.4±0.5
Northeast	8.0±0.9‡	13.0±1.0‡	18.3±0.9	20.4±0.4	18.6±0.4
U.S. citizen	79.2±1.1‡	95.4±0.5‡	97.3±0.3†	98.1±0.1	96.5±0.2
Living with both parents	66.8±1.4‡	60.9±1.3‡	43.3±1.0‡	81.5±0.4	71.7±0.4
At least one parent who works	82.1±1.1‡	82.3±1.0‡	64.5±0.9‡	94.7±0.2	87.2±0.3
Health status					
Self-reported fair or poor health	2.2±0.4‡	2.6±0.4‡	4.6±0.4‡	0.9±0.1	1.8±0.1
Chronic condition limits activity	4.9±0.7	8.3±0.7‡	12.3±0.6‡	5.1±0.2	6.7±0.2

* Plus–minus values are means ±SE.
† P<0.05 for the comparison with children who had insurance for the full year, with private coverage at the time of the interview.
‡ P<0.01 for the comparison with children who had insurance for the full year, with private coverage at the time of the interview.
§ Race or ethnic group was assigned according to data from the data-collection agency.[12]

would have problems with access to and the use of ambulatory health care. Moreover, on several measures, children who were uninsured for part of the year had problems at rates similar to those for children who were uninsured for the entire year, whereas children who had full public or private insurance coverage had much lower rates of problems.

For example, as compared with those who were privately insured all year, significantly more children who were uninsured for a full year had delayed care (odds ratio, 12.65; 95 percent confidence interval, 9.45 to 16.94), as did children who were uninsured for part of the year (odds ratio, 13.65; 95 percent confidence interval, 10.41 to 17.90). In contrast, children who were insured all year through public insurance were no different on this measure from those who were insured with private coverage.

Similarly, as compared with children who were privately insured for the full year, significantly more children who were uninsured either for part of the year (odds ratio, 7.06; 95 percent confidence interval, 5.13 to 9.69) or for the full year (odds ratio, 7.11; 95 percent confidence interval, 5.01 to 10.10) had unfilled prescriptions, whereas only slightly more children who were covered by public insurance all year had unfilled prescriptions (odds ratio, 1.47; 95 percent confidence interval, 1.01 to 2.13). Smaller but still significant effects of gaps in insurance cov-

Table 3. Association between Health Insurance Coverage for Children in the United States and Unaddressed Health Care Needs, the Existence of Usual Places for Care, and Ambulatory Visits in the Last 12 Months before They Were Interviewed for the National Health Interview Survey.*

Variable	Full-Year Uninsured	Part-Year Uninsured	Full-Year Insured, Public Coverage	Full-Year Insured, Private Coverage
		percent		
Delayed care†	15.9±1.0‡	20.2±1.2‡	2.1±0.2§	1.5±0.1
Unmet medical care¶	12.6±0.9‡	13.4±0.9‡	1.4±0.2§	0.7±0.1
Unfilled prescriptions‖	10.0±0.8‡	9.9±0.8‡	2.8±0.3§	1.0±0.1
Lack of usual places for care**	38.0±1.5‡	15.0±0.9‡	4.3±0.4§	2.8±0.2
No well-child visits††	58.7±1.5‡	37.2±1.4‡	24.2±0.8	26.3±0.5
No visits to doctors' offices‡‡	39.0±1.5‡	17.2±1.0‡	11.4±0.6	11.1±0.3

* Plus–minus values are means ±SE.
† The respondent indicated that medical care was delayed for the child because of worry about the cost.
‡ P<0.01 for the comparison with children who had insurance for the full year, with private coverage, at the time of the interview.
§ P<0.05 for the comparison with children who had insurance for the full year, with private coverage, at the time of the interview.
¶ The respondent indicated that the child needed but did not receive medical care because the family could not afford it.
‖ The respondent indicated that the child needed but did not get prescription medicines because the family could not afford it.
** The respondent indicated that the child did not have a usual place to go when sick or in need of advice about his or her health.
†† The respondent indicated that the child did not receive a well-child checkup (a general checkup when the child was not sick or injured).
‡‡ The respondent indicated that the child did not see a doctor or other medical health professional in an office, clinic, or other nonhospital or non–emergency-room setting.

erage were found for the categories of the existence of usual places for care, well-child visits, and visits to doctors' offices. Moreover, on the basis of these indicators, children with public health insurance tended to do somewhat better than those with private insurance. Many other factors in the models — income, race or ethnic group, region of residence, citizenship, family structure, and health status — were significantly related to most or all of the dependent variables, though the magnitude of these effects was notably less than the influence of insurance coverage.

DISCUSSION

According to the 2000 and 2001 National Health Interview Surveys, 6.6 percent of children in the United States were uninsured for the entire 12-month period, and an additional 7.7 percent were uninsured for part of the year. Who are the children with intermittent insurance coverage? Children uninsured for part of the year have some of the same characteristics as those uninsured for the full year. For example, 82 percent of children uninsured for the full year or part of the year have working parents.

Previous research has shown that children in low-income families and those in minority racial or ethnic groups, especially those who are Hispanic, are more likely to be uninsured than white children and children in higher-income families[16]; the same factors are related to gaps in insurance, though Hispanic children are especially at risk for being uninsured all year. The children who are uninsured for part of the year or the full year are also similar on key measures of access to health care, and they have substantially greater barriers than those who are fully insured with either public or private coverage. Parents of children in both uninsured groups were far more likely than parents of children in the fully insured groups to report delayed care, unmet medical care needs, and unfilled prescriptions for their children.

On other measures of access to health care — existence of usual places for care, well-child visits, and visits to doctors' offices — children with gaps

Table 4. Predictors of Unaddressed Health Needs for Children in the United States in the Last 12 Months before They Were Interviewed for the National Health Interview Survey.*

Variable	Delayed Care	Unmet Medical Care	Unfilled Prescriptions
	odds ratio (95% CI)		
Health insurance coverage			
Full-year uninsured	12.65 (9.45–16.94)	18.50 (13.32–25.68)	7.11 (5.01–10.10)
Part-year uninsured	13.65 (10.41–17.90)	17.05 (12.49–23.26)	7.06 (5.13–9.69)
Full-year insured, public	0.97 (0.70–1.33)	1.28 (0.85–1.94)	1.47 (1.01–2.13)
Full-year insured, private†	1.00	1.00	1.00
Age			
0 to 5 yr	0.76 (0.60–0.97)	0.68 (0.53–0.89)	0.78 (0.59–1.04)
6 to 11 yr	0.87 (0.69–1.11)	0.88 (0.67–1.16)	0.76 (0.59–0.97)
12 to 17 yr†	1.00	1.00	1.00
Family income			
Under 200% of the federal poverty level	1.37 (1.07–1.76)	1.63 (1.25–2.13)	2.29 (1.67–3.14)
200% or more of the federal poverty level†	1.00	1.00	1.00
Race or ethnic group			
Hispanic	0.56 (0.44–0.73)	0.78 (0.57–1.05)	1.13 (0.88–1.45)
Non-Hispanic black	0.79 (0.60–1.04)	0.88 (0.65–1.20)	1.12 (0.85–1.47)
Non-Hispanic other	0.58 (0.35–0.96)	0.93 (0.52–1.65)	1.10 (0.63–1.91)
Non-Hispanic white†	1.00	1.00	1.00
Region			
West	1.11 (0.82–1.50)	1.07 (0.75–1.53)	1.31 (0.88–1.95)
Midwest	1.07 (0.80–1.41)	1.24 (0.87–1.77)	1.41 (0.89–2.25)
South	0.93 (0.70–1.23)	1.19 (0.85–1.66)	1.36 (0.93–1.99)
Northeast†	1.00	1.00	1.00
Citizenship of child			
U.S.	1.66 (1.14–2.41)	1.43 (0.95–2.15)	1.53 (0.93–2.51)
Non-U.S.†	1.00	1.00	1.00
Family structure			
Living with both parents	0.63 (0.51–0.78)	0.64 (0.50–0.82)	0.71 (0.55–0.91)
Living with single parent or nonparent others†	1.00	1.00	1.00
Parental employment			
Yes	1.01 (0.79–1.30)	1.05 (0.80–1.38)	0.86 (0.66–1.12)
No†	1.00	1.00	1.00
Proxy or self-reported health status of child			
Fair or poor	2.46 (1.61–3.78)	2.10 (1.29–3.44)	2.12 (1.36–3.32)
Excellent or good†	1.00	1.00	1.00
Limitation of activity			
Yes	1.87 (1.39–2.51)	2.26 (1.63–3.12)	1.90 (1.33–2.71)
No†	1.00	1.00	1.00

* Odds ratios are adjusted. For each outcome, the model includes all variables listed in the table. In the overall model, the Wald F value was 252.85 (18 df, P<0.005) for the delayed-care group, 202.62 (18 df, P<0.005) for the unmet-medical-care group, and 197.18 (18 df, P<0.005) for the unfilled-prescriptions group. CI denotes confidence interval.
† This group served as the reference category.

Table 5. Predictors of the Lack of Usual Places for Care and Ambulatory Visits for Children in the United States in the Last 12 Months before They Were Interviewed for the National Health Interview Survey.*

Variable	Lacking Usual Places for Care	No Well-Child Visits	No Visits to Doctors' Offices
		odds ratio (95% CI)	
Health insurance coverage			
Full-year uninsured	9.82 (7.89–12.22)	3.24 (2.70–3.88)	2.92 (2.36–3.60)
Part-year uninsured	3.63 (2.93–4.49)	1.57 (1.35–1.83)	1.27 (1.06–1.52)
Full-year insured, public	0.95 (0.74–1.23)	0.85 (0.74–0.97)	0.70 (0.59–0.84)
Full-year insured, private†	1.00	1.00	1.00
Age			
0 to 5 yr	0.51 (0.42–0.61)	0.29 (0.26–0.32)	0.36 (0.31–0.42)
6 to 11 yr	0.66 (0.55–0.80)	0.95 (0.87–1.04)	0.97 (0.86–1.09)
12 to 17 yr†	1.00	1.00	1.00
Family income			
Under 200% of the federal poverty level	1.61 (1.34–1.94)	1.31 (1.17–1.47)	1.74 (1.50–2.01)
200% or more of the federal poverty level†	1.00	1.00	1.00
Race or ethnic group			
Hispanic	1.48 (1.20–1.83)	0.85 (0.76–0.95)	1.33 (1.15–1.54)
Non-Hispanic black	0.99 (0.78–1.26)	0.66 (0.57–0.75)	1.25 (1.07–1.46)
Non-Hispanic other	1.49 (1.08–2.08)	0.80 (0.65–0.99)	1.34 (1.01–1.78)
Non-Hispanic white†	1.00	1.00	1.00
Region			
West	3.50 (2.62–4.69)	3.42 (2.88–4.08)	2.44 (1.99–3.00)
Midwest	2.83 (2.08–3.85)	2.67 (2.24–3.18)	1.80 (1.49–2.18)
South	3.05 (2.33–3.99)	2.83 (2.40–3.34)	2.21 (1.84–2.64)
Northeast†	1.00	1.00	1.00
Citizenship of child			
U.S.	0.38 (0.29–0.50)	0.79 (0.64–0.98)	0.69 (0.55–0.87)
Non-U.S.†	1.00	1.00	1.00
Family structure			
Living with both parents	0.77 (0.65–0.91)	0.93 (0.84–1.03)	0.93 (0.82–1.07)
Living with single parent or nonparent others†	1.00	1.00	1.00
Parental employment			
Yes	0.99 (0.78–1.25)	1.01 (0.88–1.16)	1.01 (0.85–1.21)
No†	1.00	1.00	1.00
Proxy or self-reported health status of child			
Fair or poor	0.79 (0.49–1.29)	1.11 (0.84–1.48)	0.49 (0.31–0.79)
Excellent or good†	1.00	1.00	1.00
Limitation of activity			
Yes	1.02 (0.73–1.42)	0.77 (0.66–0.91)	0.60 (0.47–0.77)
No†	1.00	1.00	1.00

* Odds ratios are adjusted. For each outcome the model includes all variables listed in the table. In the overall model, the Wald F value was 278.14 (18 df, P<0.005) for the group lacking usual places for care, 151.47 (18 df, P<0.005) for the group with no well-child visits, and 296.91 (18 df, P<0.005) for the group with no visits to doctors' offices. CI denotes confidence interval.
† This group served as the reference category.

in insurance coverage fell between those with full-year private insurance and those who were uninsured for the full year. Having a usual source of care is the foundation for the pediatric concept of a "medical home."[17] Therefore, the risk of going without a usual source of care, which is associated with decreased use of preventive care and increased use of emergency departments for nonemergency conditions, is of particular concern.[18-20]

Children with year-long public insurance coverage had unaddressed health needs, lacked usual places for care, and used ambulatory health care services at rates that were nearly indistinguishable from the rates for children with year-long private insurance. Indeed, in the multivariate models, children with full-year public insurance coverage had a slightly better outcome for well-child care than did those with full-year private coverage. Hence, it seems that continuity is more important than the type of coverage in terms of access to care. Continuous coverage, whether public or private, conveys important protections and is superior to intermittent coverage or no coverage at all. Notably, in the multivariate analysis, although family income and race or ethnic group had independent effects on most measures, insurance status was a substantially more powerful predictor of access to and use of health care for children.

The limitations of this study should be noted. Our categorization of insurance coverage does not distinguish children who had mixed public and private insurance during the year; however, the four categories we use seem to represent distinct groups. The National Health Interview Survey also provides data on insurance coverage and access only during a 12-month span; this probably leads to an underestimation of the number of children having problems. On the basis of data from the 1990s, Short and Graefe found that during a four-year period, more than 40 percent of children had at least one gap in insurance coverage.[6] Nevertheless, the effect of discontinuous insurance coverage on access to and the use of health care may be overstated in our correlational analysis to the extent that greater health care needs compel families to maintain insurance on a continuous basis.

Our findings raise questions that are beyond the scope of this article but suggest issues that should be further explored. Analyses incorporating multiple sets of data are needed to examine fully the causes and consequences of gaps in insurance coverage. For example, the findings that health insurance coverage for Hispanic children differs substantially from that for children in other racial or ethnic groups and that coverage and access vary across geographic regions point to the need to study regional and state differences to explore the dynamics that lead to problems with health insurance coverage and access. The reasons that gaps in insurance coverage have greater effects on some measures than on others also needs further study. It may be that families who have insurance coverage for part of the year visit the doctor during periods of coverage, but they are as disadvantaged as those with no insurance coverage with respect to continuity of care.

A careful reading of most policy reports will show that when the number of persons in the United States without insurance is reported, the calculations used to produce that number are usually not articulated. However, estimates at a single point in time are typically presented.[3-5,8] Such estimates exclude many persons with gaps in coverage and underestimate the number of uninsured persons in the United States. The problem of the "hidden uninsured" has clear implications for both policy and research. For researchers, the findings emphasize that categorizing insurance coverage as a dichotomy is overly simplistic. Given the complexity of the ways in which families gain and lose insurance coverage and the effects of those discontinuities, multidimensional definitions of coverage should be incorporated into analyses. In studies of the magnitude and the effects of health insurance problems, researchers should clearly explain how the uninsured are defined, consider the implications of the analyses, and discuss how limitations in the measures may affect the findings.

For policymakers, the findings point to the need for more encompassing measures of the situation of being uninsured. Gaps in insurance coverage have, to an extent, been viewed as a problem that corrects itself or is a minor issue relative to a long-term lack of insurance. However, we have found that on several indicators, children with intermittent insurance have notable problems. They do not get medical care, they do not get prescriptions filled, or they go without preventive care visits. Such issues need to be incorporated into policy discussions to estimate accurately the scope of insurance problems and to develop policy options that are sensitive to the ways children get and keep insurance coverage.

Supported by the American Academy of Pediatrics.

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CLINICAL PRACTICE

Cervical Radiculopathy

Simon Carette, M.D., M.Phil., and Michael G. Fehlings, M.D., Ph.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 37-year-old woman presents with a two-week history of severe neck pain radiating to her left shoulder girdle and extending to the arm, forearm, and dorsum of the hand. She reports having had no fever, weight loss, leg weakness, or urinary or bowel dysfunction. Physical examination reveals weakness of her left triceps, finger extensors, and wrist flexors, as well as hypoesthesia of the third digit and a diminished triceps reflex. How should her case be managed?

THE CLINICAL PROBLEM

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N Engl J Med 2005;353:392-9.

Cervical radiculopathy is a neurologic condition characterized by dysfunction of a cervical spinal nerve, the roots of the nerve, or both. It usually presents with pain in the neck and one arm, with a combination of sensory loss, loss of motor function, or reflex changes in the affected nerve-root distribution.[1]

EPIDEMIOLOGY

Population-based data from Rochester, Minnesota, indicate that cervical radiculopathy has an annual incidence rate of 107.3 per 100,000 for men and 63.5 per 100,000 for women, with a peak at 50 to 54 years of age.[2] A history of physical exertion or trauma preceded the onset of symptoms in only 15 percent of cases. A study from Sicily reported a prevalence of 3.5 cases per 1000 population.[3]

Data on the natural history of cervical radiculopathy are limited.[2,4-6] In the population-based study from Rochester, Minnesota, 26 percent of 561 patients with cervical radiculopathy underwent surgery within three months of the diagnosis (typically for the combination of radicular pain, sensory loss, and muscle weakness), whereas the remainder were treated medically.[2] Recurrence, defined as the reappearance of symptoms of radiculopathy after a symptom-free interval of at least 6 months, occurred in 32 percent of patients during a median follow-up of 4.9 years. At the last follow-up, 90 percent of the patients had normal findings or were only mildly incapacitated owing to cervical radiculopathy.

CAUSES AND PATHOPHYSIOLOGICAL FEATURES

The most common cause of cervical radiculopathy (in 70 to 75 percent of cases) is foraminal encroachment of the spinal nerve due to a combination of factors, including decreased disc height and degenerative changes of the uncovertebral joints anteriorly and zygapophyseal joints posteriorly (i.e., cervical spondylosis) (Fig. 1). In contrast to disorders of the lumbar spine, herniation of the nucleus pulposus is responsible for only 20 to 25 percent of cases.[2] Other causes, including tumors of the spine and spinal infections, are infrequent.[7]

The mechanisms underlying radicular pain are poorly understood. Nerve-root compression by itself does not always lead to pain unless the dorsal-root ganglion is

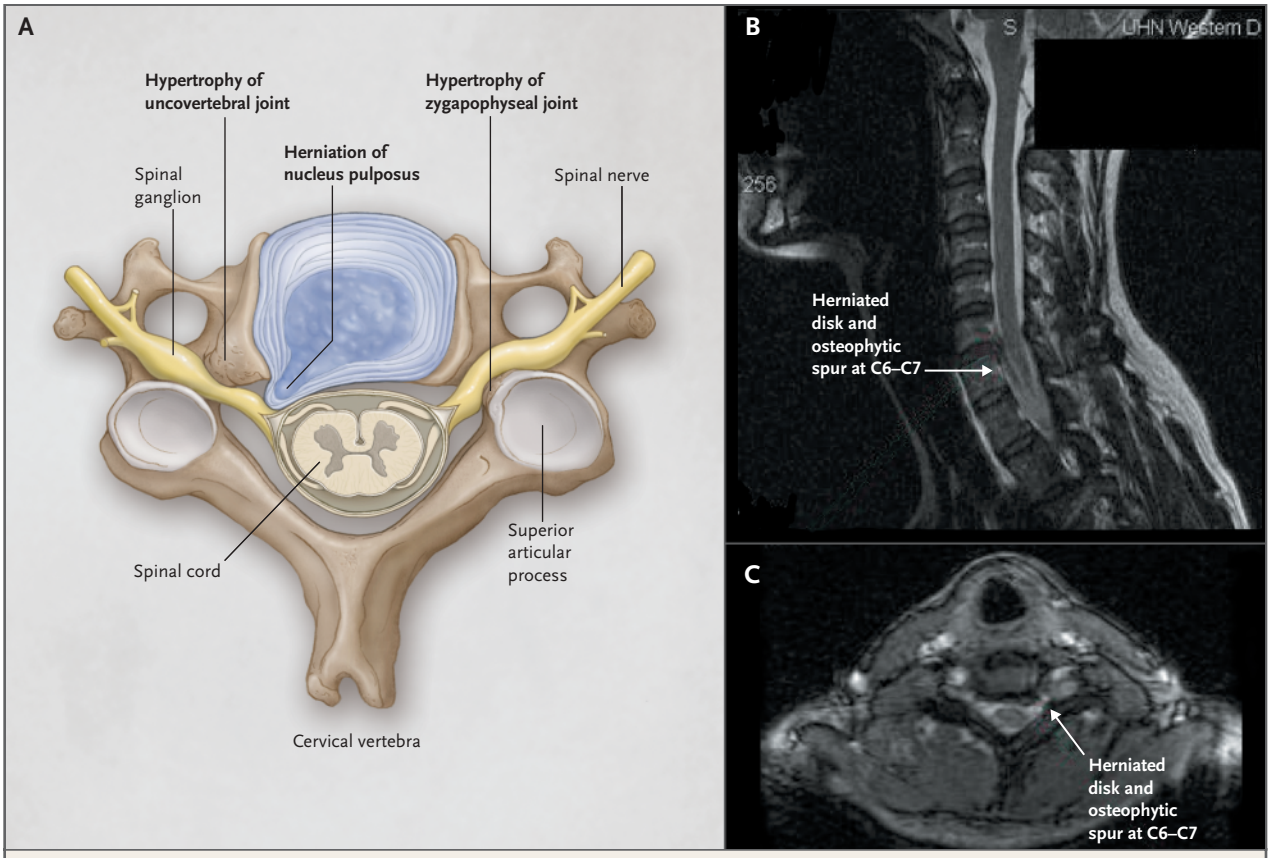

Figure 1. Causes of Cervical Radiculopathy.

Foraminal encroachment of the spinal nerve from degenerative changes in the uncovertebral and zygapophyseal joints and herniation of the nucleus pulposus are the two most common causes of cervical radiculopathy (Panel A). T_2-weighted magnetic resonance imaging in a sagittal view (Panel B) and axial view (Panel C) shows a herniated disk and an osteophytic spur at C6–C7 paracentral to the left side with compression of the exiting C7 nerve root. There is no evidence of spinal cord compression.

also compressed.[8,9] Hypoxia of the nerve root and dorsal ganglion can aggravate the effect of compression.[10] Evidence from the past decade indicates that inflammatory mediators — including matrix metalloproteinases, prostaglandin E_2, interleukin-6, and nitric oxide — are released by herniated cervical intervertebral disks.[11-13] These observations provide a rationale for treatment with antiinflammatory agents.[14] In patients with disk herniation, the resolution of symptoms with nonsurgical management correlates with attenuation of the herniation on imaging studies.[15-18]

STRATEGIES AND EVIDENCE

CLINICAL DIAGNOSIS

There are no universally accepted criteria for the diagnosis of cervical radiculopathy.[19] In most cases, the patient's history and physical examination are sufficient to make the diagnosis.[20] Typically, patients present with severe neck and arm pain. Although the sensory symptoms (including burning, tingling, or both) typically follow a dermatomal distribution, the pain is more commonly referred in a myotomal pattern.[2,21] For example, radicular pain from C7 is usually perceived deeply through the shoulder girdle with extension to the arm and forearm, whereas numbness and paresthesias are more commonly restricted to the central portion of the hand, the third digit, and occasionally the forearm. Subjective weakness of the arm or hand is reported less frequently. Holding the affected arm on top of the head[22] or moving the head to look down and away from the symptomatic side often improves the pain, whereas rotation of the head or bending it toward the symptomatic side increases the pain.[23]

Guidelines developed by the Agency for Health Care Policy and Research for the assessment of

low back pain may be applied to the patient with neck pain and radiculopathy.[24] The presence of "red flags" in the patient's history (including fever, chills, unexplained weight loss, unremitting night pain, previous cancer, immunosuppression, or intravenous drug use) should alert clinicians to the possibility of more serious disease, such as tumor or infection. Clinicians should also inquire about symptoms of myelopathy. These may occasionally be subtle (e.g., diffuse hand numbness and clumsiness, which are often attributed to peripheral neuropathy or carpal tunnel syndrome; difficulty with balance; and sphincter disturbances presenting initially as urinary urgency or frequency rather than as retention or incontinence).

Findings on physical examination vary depending on the level of radiculopathy and on whether there is myelopathy (Tables 1 and 2). In most series, the nerve root that is most frequently affected is the C7, followed by the C6.[2] Many provocative tests have been proposed for the diagnosis of cervical radiculopathy, but the reliability and diagnostic accuracy of these tests are poor.[19,25]

Several conditions can mimic cervical radiculopathy and should be ruled out by history taking and physical examination, occasionally supplemented by imaging, electrophysiological studies, or both[26] (Table 3).

LABORATORY STUDIES

Laboratory studies are of limited value and are not recommended. The erythrocyte sedimentation rate and C-reactive protein levels are elevated in many patients with spinal infection or cancer, but these tests are not sufficiently sensitive or specific to guide further evaluation.

IMAGING

Conventional radiographs of the cervical spine are often obtained, but their usefulness is limited.[31] This is due to the low sensitivity of radiography for the detection of tumors or infections, as well as its inability to detect disk herniation and the limited value of the finding of cervical intervertebral narrowing in predicting nerve-root or cord compression.[32]

Magnetic resonance imaging (MRI) is the approach of choice when imaging is pursued in patients with cervical radiculopathy (Fig. 1),[33] but there are currently no clear guidelines regarding when such imaging is warranted. Reasonable indications include the presence of symptoms or signs of myelopathy, red flags suggestive of tumor or infection, or the presence of progressive neurologic deficits. For most other patients, it is appropriate to limit the use of MRI to those who remain symptomatic after four to six weeks of nonsurgical treatment, particularly given the high frequency of abnormalities detected in asymptomatic adults, including disk herniation or bulging (57 percent of cases), spinal cord impingement (26 percent), and cord compression (7 percent).[34]

Computed tomography (CT) alone is of limited value in assessing cervical radiculopathy,[35] but it can be useful in distinguishing the extent of bony spurs, foraminal encroachment, or the presence of

Table 1. Physical Findings Associated with Cervical Radiculopathy.*

Disk Level	Root	Pain Distribution	Weakness	Sensory Loss	Reflex Loss
C4–C5	C5	Medial scapular border, lateral upper arm to elbow	Deltoid, supraspinatus, infraspinatus	Lateral upper arm	Supinator reflex
C5–C6	C6	Lateral forearm, thumb and index finger	Biceps, brachioradialis, wrist extensors	Thumb and index finger	Biceps reflex
C6–C7	C7	Medial scapula, posterior arm, dorsum of forearm, third finger	Triceps, wrist flexors, finger extensors	Posterior forearm, third finger	Triceps reflex
C7–T1	C8	Shoulder, ulnar side of forearm, fifth finger	Thumb flexors, abductors, intrinsic hand muscles	Fifth finger	—

* Provocative tests include the foraminal compression test (Spurling maneuver), in which the neck is passively bent toward the symptomatic side and the examiner applies pressure (approximately 7 kg) to the patient's head (a positive test reproduces symptoms); the shoulder abduction test, in which the patient is asked to place the hand of the symptomatic arm on the head (a positive test reduces or eliminates symptoms); and the neck distraction test, in which the patient is supine and the examiner, holding the chin and occiput, applies a gradual pulling force (a positive test reduces or eliminates symptoms).[25]

ossification of the posterior longitudinal ligament. The combination of CT with the intrathecal administration of contrast material (CT myelography) provides accuracy similar to[36] and possibly superior to[37] that of MRI, but its invasive nature makes MRI preferable in most cases. Technetium and gallium bone scans are very seldom indicated, except in rare cases in which cancer or infection is suspected in multiple sites and MRI cannot be readily performed or is impractical.

Table 2. Physical Findings Associated with Myelopathy.

Findings
Hyperreflexia; hypertonia; clonus of the ankle, knee, or wrist; pathological reflexes or signs, such as the Babinski sign, Hoffmann's sign (flexion and adduction of the thumb when the examiner flexes the terminal phalanx of the long finger), and Lhermitte's sign (a sensation of electrical shock radiating down the spine, precipitated by neck flexion)
Clinical grading*
Mild
Sensory symptoms; subjective weakness; hyperreflexia (with or without Hoffmann's sign or the Babinski sign); no functional impairment
Moderate
Objective motor or sensory signs (a score of >4 out of 5 on the Medical Research Council scale); either no or mild functional impairment (e.g., mild slowing of gait)
Severe
Objective motor or sensory signs with functional impairment (e.g., hand weakness, unsteady gait, sphincter disturbance)

* Clinical grading is performed on the basis of the extent of symptoms, signs, and functional impairment.

ELECTRODIAGNOSTIC STUDIES

Needle electromyography and nerve-conduction studies can be helpful when the patient's history and physical examination are inadequate to distinguish cervical radiculopathy from other neurologic causes of neck and arm pain. Typically, abnormal insertional activity, including positive sharp-wave potentials and fibrillation potentials, is present in the limb muscles of the involved myotome within three weeks of the onset of nerve compression.[38] Examination of the paraspinal muscles increases the sensitivity of the test, since insertional activity can be seen as early as 10 days after the nerve injury. In addition, the presence of abnormal findings in paraspinal muscles differentiates cervical radiculopathy from brachial plexopathy.

TREATMENT

Nonsurgical Management

The main objectives of treatment are to relieve pain, improve neurologic function, and prevent recurrences.[39] None of the commonly recommended nonsurgical therapies for cervical radiculopathy has been tested in randomized, placebo-controlled trials. Thus, recommendations derive largely from case series and anecdotal experience. The preferences of patients should be taken into account in decision making.

On the basis of anecdotal experience, analgesic agents, including opioids and nonsteroidal antiinflammatory drugs, are often used as first-line therapy. In patients with acute pain, some physicians advocate a short course of prednisone (for example, starting at a dose of 70 mg per day and decreasing by 10 mg every day).[39] This practice is supported only by anecdotal evidence, however, and is associated with potential risks.

Retrospective[40,41] and prospective[42,43] cohort studies have reported favorable results with translaminar and transforaminal epidural injections of corticosteroids, with up to 60 percent of patients reporting long-term relief of radicular and neck pain and a return to usual activities. However, complications from these injections, although rare, can be serious and include severe neurologic sequelae from spinal cord or brainstem infarction.[44] Given the potential for harm, placebo-controlled trials are urgently needed to assess both the safety and the efficacy of cervical epidural injections.

Some investigators have advocated the use of short-term immobilization (less than two weeks) with either a hard or a soft collar (either continuously or only at night) to aid in pain control.[45] Use of a cervical pillow during sleep has also been recommended. However, data are needed to assess the benefits of these approaches.

Cervical traction consists of administering a distracting force to the neck in order to separate the cervical segments and relieve compression of nerve roots by intervertebral disks. Various techniques (supine vs. sitting; intermittent vs. sustained; motorized or hydraulic vs. an over-the-door pulley with weights) and durations (minutes vs. up to an hour) have been recommended.[46,47] However, a systematic review stated that no conclusions could be drawn about the efficacy of cervical traction because of the poor methodologic quality of the available data.[48] Exercise therapy — including active range-of-motion exercises and aerobic conditioning (walking or use of a stationary bicycle), followed by isometric and progressive-resistive exercises — is typically recommended once pain has subsided

Table 3. Conditions with Physical Findings Mimicking Those of Cervical Radiculopathy.

Condition	Findings
Peripheral entrapment neuropathies (e.g., carpal tunnel syndrome)	Hypoesthesia and weakness in the distribution of the entrapped nerve (e.g., in carpal tunnel syndrome, medial three digits and opponens pollicis; in ulnar entrapment, fourth and fifth digits and thumb adductor); Tinel's sign and positive Phalen's maneuver often present in carpal tunnel syndrome; normal reflexes; nerve-conduction studies abnormal in carpal tunnel syndrome but normal in cervical radiculopathy
Disorders of the rotator cuff and shoulder	Pain in the shoulder or lateral arm region that only rarely radiates below the elbow and is aggravated by active and resisted shoulder movements, rather than by neck movements; normal sensory examination and reflexes
Acute brachial-plexus neuritis (neuralgic amyotrophy or Parsonage–Turner syndrome)	Typically causes severe pain in neck, shoulder, and arm, which is followed within days to a few weeks by marked arm weakness, typically in the C5–C6 region, as the pain recedes[27,28] (unlike in cervical radiculopathy, in which pain and neurologic findings occur simultaneously)
Thoracic outlet syndrome	Pain in shoulder and arm aggravated by use of the arm; intermittent paresthesia, most commonly in the C8–T1 region (rare in cervical radiculopathy); reproduction of symptoms by provocation tests, including Roo's test (the rapid flexion and extension of fingers while the arms are abducted at 90° and externally rotated 90°); neurologic examination usually normal; decreased radial pulse if associated with vascular compression (rare); nerve-conduction studies usually normal
Herpes zoster	Neuropathic pain in a dermatomal distribution, followed within several days by the appearance of the typical vesicular rash
Pancoast syndrome	Pain in shoulder and arm due to compression of the brachial plexus; paresthesia and weakness in the C8–T1 region (intrinsic hand muscles); ipsilateral ptosis, myosis, and anhydrosis (Horner's syndrome)
Sympathetically mediated syndromes	Diffuse pain and burning in arm and hand associated with swelling, hyperesthesia, allodynia, and vasomotor changes (temperature and color); neurologic examination usually normal
Referred somatic pain from the neck	Pain referred from cervical structures, including the intervertebral disks and zygapophyseal joints, that is usually felt in a segmental distribution (i.e., structures from the C5–C6 level, posterior neck, and supraspinatus fossa; C6–C7 level, supraspinatus fossa and scapula). Unlike in cervical radiculopathy, the pain is rarely felt below the elbow and the neurologic examination is normal[29,30]

in order to reduce the risk of recurrence, although this recommendation is not supported by evidence from clinical trials.[39]

SURGERY

In appropriate patients, surgery may effectively relieve otherwise intractable symptoms and signs related to cervical radiculopathy, although there are no data to guide the optimal timing of this intervention.[4,5] Commonly accepted indications for surgery differ depending on whether the patient has evidence of radiculopathy alone or whether there are also signs of spinal cord impairment, since the latter can lead to progressive and potentially irreversible neurologic deficits over time.

For cervical radiculopathy without evidence of myelopathy, surgery is typically recommended when all of the following are present: definite cervical-root compression visualized on MRI or CT myelography; concordant symptoms and signs of cervical-root–related dysfunction, pain, or both; and persistence of pain despite nonsurgical treatment for at least 6 to 12 weeks or the presence of a progressive, functionally important motor deficit. Common surgical procedures for cervical radiculopathy are shown in Figure 2.[49] Randomized trials are lacking to compare these approaches.

Surgery is also recommended in cases in which imaging shows cervical compression of the spinal cord and there is clinical evidence of moderate-to-severe myelopathy (Table 2). For such patients, anterior approaches (preferred in patients with a cervical kyphosis) include cervical diskectomy and corpectomy (removal of the central portion of the vertebral body) alone or in combination at single or multiple levels. Anterior decompression is generally combined with a strut reconstruction (bridging the space between the end plates of the verte-

bral bodies) with the use of bone (either autograft or allograft) or synthetic materials (carbon fiber or titanium cages) and plate fixation. Posterior options, which are often used in cases of multilevel decompressions in which there is preserved cervical lordosis, include laminectomy (with or without instrumented fusion) and laminoplasty (involving decompression and reconstruction of the laminae).

Data from prospective observational studies indicate that two years after surgery for cervical radiculopathy without myelopathy, 75 percent of patients have substantial relief from radicular symptoms (pain, numbness, and weakness).[50,51] Corresponding response rates for relief of radicular arm pain after surgery appear similar in patients treated for cervical myelopathy.[52]

Complications of surgery for cervical radiculopathy with or without myelopathy are uncommon but can include iatrogenic injury to the spinal cord (occurring in less than 1 percent of cases), nerve-root injury (2 to 3 percent), recurrent nerve palsy (hoarseness, 2 percent after anterior cervical surgery), esophageal perforation (less than 1 percent), and failure of instrumentation (breakage or loosening of a screw or plate or nonunion, less than 5 percent for single-level surgery).[50-52]

SURGICAL VS. NONSURGICAL MANAGEMENT

As summarized in a recent Cochrane review,[53] there are few good-quality studies comparing surgical and nonsurgical treatments for cervical radiculopathy. In one randomized trial comparing surgical and nonsurgical therapies among 81 patients with radiculopathy alone, the patients in the surgical group had a significantly greater reduction in pain at three months than the patients who were assigned to receive physiotherapy or who underwent immobilization in a hard collar (reductions in visual-analogue scores for pain: 42 percent, 18 percent, and 2 percent, respectively).[54] However, at one year, there was no difference among the three treatment groups in any of the outcomes measured, including pain, function, and mood.

In patients with mild signs of cervical myelopathy (not meeting the above criteria for surgery), nonsurgical treatment is reasonable. This recommendation is supported by the results of a small, but otherwise well-designed, randomized trial in-

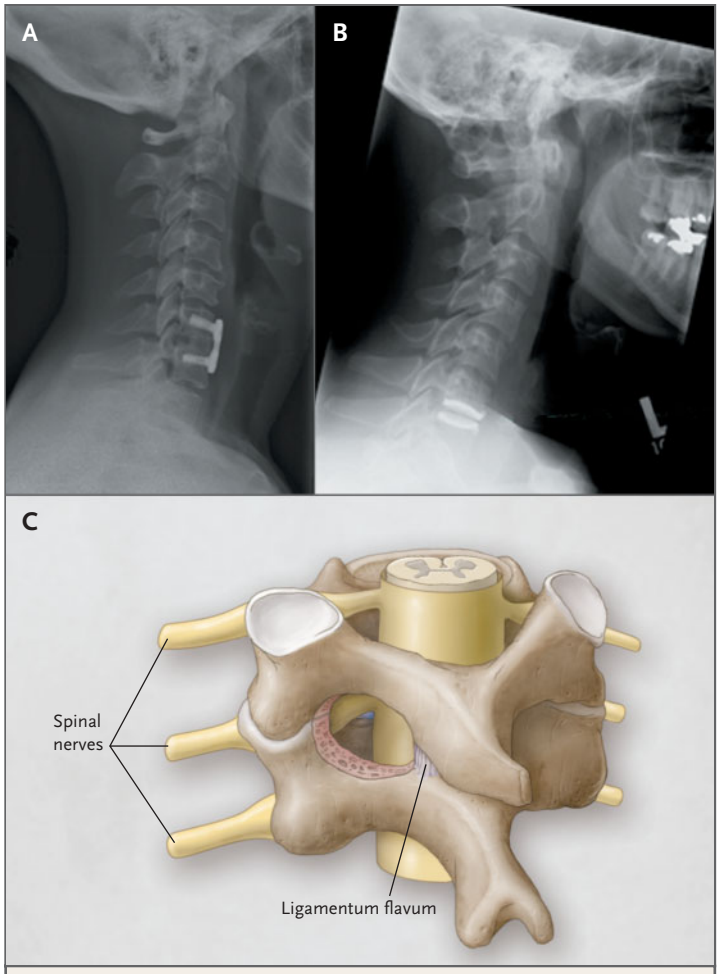

Figure 2. Surgical Approaches for the Treatment of Cervical Radiculopathy.
Anterior cervical diskectomy (Panel A) can be performed without spinal fusion, although more commonly a fusion (using a variety of biologic and synthetic materials) is performed to prevent disk collapse and kyphosis. As illustrated in the figure, this is commonly accompanied by anterior fixation of a plate to facilitate early return to normal activity. Anterior foraminotomy without fusion is a possible alternative, but there is less clinical experience with this option. In cervical arthroplasty (Panel B), an artificial disk made of various synthetic materials is inserted into the evacuated disk space after anterior cervical diskectomy has been performed. This procedure (which is not approved by the Food and Drug Administration) is used outside the United States as an alternative to fusion in an effort to preserve motion and to minimize adjacent segment degeneration. Small prospective case series show results approximately equivalent to those with fusion at one-year follow-up, although randomized trials are lacking to show that arthroplasty results in less adjacent segment degeneration than does fusion.[49] Posterior laminoforaminotomy (Panel C) consists of a posterior decompression of the exiting cervical nerve root by partial removal of the lamina and medial facet and partial removal of the disk or osteophytic spurs. This procedure is indicated only for a condition that is laterally placed (not for central stenosis).

volving 51 patients, which showed that at two-year follow-up, no differences in neurologic outcomes were observed between patients treated medically and those treated surgically.[55]

AREAS OF UNCERTAINTY

The natural history of cervical radiculopathy remains uncertain. Data are needed from well-designed, randomized, controlled trials to guide nonsurgical management and decisions regarding whether and when to perform surgery.

GUIDELINES

There are no published guidelines by professional societies for the assessment and management of cervical radiculopathy.

SUMMARY AND RECOMMENDATIONS

Patients who present with acute neck and arm pain suggestive of cervical radiculopathy, such as the woman described in the vignette, should be assessed first by a careful history taking and physical examination. In the absence of red flags suggesting infection or cancer or signs of myelopathy, it is reasonable to defer imaging and treat the patient's pain with analgesics (usually, nonsteroidal antiinflammatory drugs). MRI is indicated if substantial pain is still present four to six weeks after the initiation of treatment or if there are progressive neurologic deficits. Other options include cervical traction or transforaminal injections of corticosteroids, although the latter have potential risks, and neither approach has been well studied. It is reasonable to recommend a progressive exercise program once pain is under control, although it remains uncertain whether such a program reduces the risk of recurrence. Surgery should be reserved for patients who have persistent and disabling pain after at least 6 to 12 weeks of nonsurgical management, progression of neurologic deficits, or signs of moderate-to-severe myelopathy.

Dr. Carette reports having received consulting fees from Novartis and Pfizer; and Dr. Fehlings, consulting fees from DePuy Spine and Synthes. Dr. Fehlings is partially supported by the Krembil Chair in Neural Repair and Regeneration.

We are indebted to Drs. Thomas Drucker, James Weinstein, and Alexander Vaccaro for reviewing earlier drafts of the manuscript; and to Dr. Eric Massicotte for providing data for a figure.

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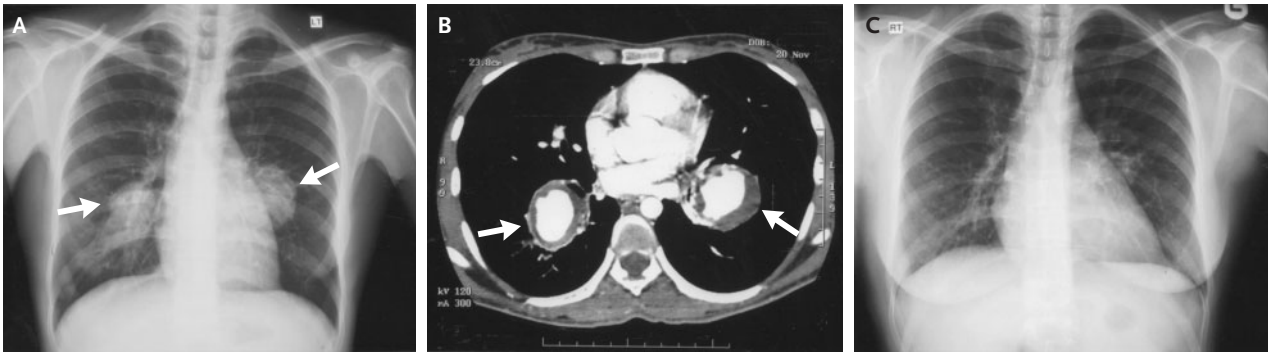
IMAGES IN CLINICAL MEDICINE

Bilateral Pulmonary-Artery Aneurysms in Behçet's Syndrome



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Wythenshawe Hospital
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A 28-year-old Asian woman presented with pyrexia of unknown origin, oral and genital ulcers, and hemoptysis. A chest radiograph showed bilateral central hilar opacities (Panel A, arrows). A computed tomographic scan of the chest showed bilateral pulmonary-artery aneurysms with associated thickening of the vessel wall and contrast enhancement consistent with edema, which is likely to be associated with thrombosis (Panel B, arrows). The patient was given a diagnosis of Behçet's syndrome and was treated with prednisolone and pulse cyclophosphamide. A follow-up chest radiograph (Panel C), obtained 18 months after she began the immunosuppressive treatment, showed resolution of the pulmonary-artery aneurysms. Behçet's syndrome is classically associated with recurrent oral and genital ulcerations and uveitis; however, it is a multisystem disease that may have intestinal, articular, neurologic, and vascular involvement.

Web-only Images in Clinical Medicine are published every week in the *Journal*. They are listed (with e page numbers) in the table of contents on the cover of the printed *Journal* and can be seen at **www.nejm.org**.

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 23-2005: A 57-Year-Old Man with a Mass in the Liver

Kenneth K. Tanabe, M.D., Lawrence S. Blaszkowsky, M.D., Raymond T. Chung, M.D., Michael A. Blake, M.D., and Gregory Y. Lauwers, M.D.

PRESENTATION OF CASE

A 57-year-old man was admitted to the hospital because of a mass in the liver.

The patient had been well until approximately two years before admission, when a diagnosis of chronic active hepatitis associated with hepatitis B virus (HBV) infection was made at another hospital. Lamivudine was started one year before admission; the results of liver-function tests returned to normal after the treatment was initiated, and the viral load fell. A surveillance ultrasonograpic examination of the abdominal area performed five months before admission revealed a mass, 3 cm in diameter, in the right lobe of the liver. Four months before admission, computed tomographic (CT) scanning and magnetic resonance imaging (MRI) of the abdominal area documented a mass, 4 cm in diameter, in the dome of the right lobe of the liver. Multiple cysts were also present.

Two months before admission, a percutaneous fine-needle aspiration biopsy of the liver was performed at another hospital; pathological examination of a specimen revealed a poorly differentiated carcinoma, thought to be hepatocellular carcinoma, cholangiocarcinoma, or metastatic carcinoma. The patient was evaluated at another hospital for liver transplantation, and it was determined that he was eligible, but his Model for End-Stage Liver Disease (MELD) score[1] was low and it was unlikely that he would receive a transplant within the next six months.

Six weeks before admission, the patient was referred to the gastrointestinal cancer center at this hospital. He had lost 1.4 kg in the preceding five months but felt well. His medications were loratadine and lamivudine. He had undergone a cholecystectomy nine years earlier. He had a history of 10 pack-years of smoking but had stopped two years earlier; he rarely drank alcohol and did not abuse intravenous drugs. He was a native of China and had immigrated to the United States fifteen years earlier. He was married with two children, who were well. His father was alive and well in his eighties, his mother had died in her seventies from congestive heart failure, and two of his five siblings were known to have hepatitis B infection.

On physical examination, the patient was a slender man who appeared to be well and without jaundice. His vital signs were normal. His performance status was 0, on a scale from 0 to 5 (with 0 indicating no adverse effects on his activity from the disease and 5 indicating death). The physical examination revealed no abnormalities. The re-

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N Engl J Med 2005;353:401-10.

sults of a complete blood count and the serum levels of glucose, electrolytes, albumin, globulin, and bilirubin were all within the normal range, as were the results of renal-function and coagulation tests. The level of alanine aminotransferase was 135 U per liter and that of aspartate aminotransferase was 78 U per liter. The level of carcinoembryonic antigen was 1.6 ng per milliliter (1.6 μg per liter), and the alpha-fetoprotein level was 2.6 ng per milliliter (2.6 μg per liter).

Chest, abdominal, and pelvic CT scanning revealed an enhancing mass (Fig. 1), 4.7 cm by 4.5 cm, within the right lobe of the liver and multiple hepatic cysts. There was no evidence of metastatic disease. MRI scanning of the liver showed simple cysts and an arterially enhancing, encapsulated lesion, 4.7 cm by 4.5 cm, straddling the right and left lobes of the liver.

The patient was admitted to the hospital and a diagnostic procedure was performed.

DISCUSSION OF MANAGEMENT

Dr. Michael A. Blake: Axial enhanced CT images were obtained during several phases after the administration of intravenous contrast material, including the arterial phase (Fig. 1A), portal venous phase, and delayed phase (Fig. 1B). These images, from an examination that had been performed approximately five weeks before admission, show a round mass, 4.7 cm by 4.5 cm, in the dome of the liver. They show heterogeneous arterial enhancement, heterogeneous enhancement on the portal venous phase, and delayed peripheral rim enhancement of a capsule. The mass straddles the middle hepatic vein, but there is no evidence of venous invasion, lymphadenopathy, or cirrhosis.

T_1- and T_2-weighted MRI scans show that the mass is hypointense relative to the liver (on the T_1-weighted images) with a faint hypointense capsule, and slightly hyperintense relative to the liver on the T_2-weighted images (Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). After the administration of gadolinium, T_1-weighted images reveal heterogeneous central enhancement of the mass on arterial-phase images, heterogeneous enhancement on portal venous–phase images, and capsular enhancement (Fig. 2 of the Supplementary Appendix). There is no evidence of venous invasion or cirrhosis.

The information provided by MRI with gadolinium is similar to that of triphasic CT scanning with regard to tumor enhancement and, in addition, provides greater intrinsic information about tissue characteristics; thus, gadolinium-enhanced MRI is the imaging method of choice for characterization of hepatic lesions.[2] The overall appearance of this lesion is most consistent with a hepatocellular carcinoma in a patient with hepatitis. Other tumors that have a similar appearance on imaging, but less commonly, include an adenoma and, rarely, a hypervascular metastasis.

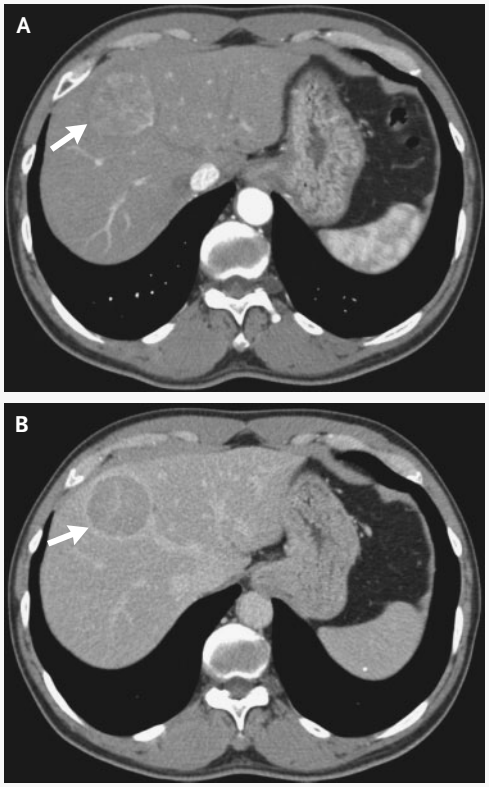


Figure 1. Axial CT Images of the Liver.

An arterial-phase CT image (Panel A), obtained after the administration of contrast material, shows heterogeneous arterial enhancement and a hepatic mass, 4.7 cm by 4.5 cm (arrow). In the delayed-phase CT image (Panel B), the mass shows delayed enhancement of a peripheral capsule (arrow). The mass straddles the middle hepatic vein and is located in both segments IV and VIII of the liver. No gross venous invasion or evidence of cirrhosis is seen in the image.

HEPATITIS B INFECTION AND HEPATOCELLULAR CARCINOMA

Dr. Raymond T. Chung: This patient had chronic active HBV infection. He had emigrated from China,

where HBV is endemic. He is likely to have contracted HBV perinatally, since two of his siblings were also infected. Epidemiologic studies have firmly identified chronic infection with HBV as a major risk factor for the development of hepatocellular carcinoma.[3]

HBV, a member of the family Hepadnaviridae, is a partially double-stranded DNA virus, the genome of which contains four partially open reading frames that overlap. These frames encode the pre-S1-S2-S, precore–core, polymerase, and X proteins. The pre-S1-S2-S gene product is processed to become hepatitis B surface antigen (HBsAg); the secretion of HBsAg from hepatocytes indicates chronic infection. In most cases, the gene products from the precore or core region yield secreted hepatitis B e antigen (HBeAg), a marker of active replication that can also be confirmed by molecular tests for circulating HBV DNA. Perinatal exposure to HBV is associated with high rates (90 percent) of chronic infection, which may alternate between replicative and nonreplicative phases.

A diagnosis of hepatocellular carcinoma was made in this patient a few months before admission. HBV contributes to hepatocarcinogenesis through several mechanisms (Fig. 2).[4] HBV can be integrated into the DNA of the host chromosomes, where random insertion adjacent to proto-oncogenes or tumor-suppressor genes could activate proliferative pathways. In addition, the HBV X protein may itself be oncogenic.[5] Finally, active viral replication in the liver causes a necrotizing inflammatory response, with necrosis and regeneration of hepatocytes, that results in an increase in the risk of the accumulation of mutations that contribute to malignant transformation.[6] Fibrosis and cirrhosis ultimately develop; in general, hepatic cirrhosis from most causes is associated with an increased risk of hepatocellular carcinoma. The risk of hepatocellular carcinoma was increased 10 times among HBsAg-positive men in a recent study, as compared with those who were not HBsAg-positive, and 60 times among men who were both HBsAg-positive and HBeAg-positive, as compared with those who were not; this risk of cancer increased with age.[7]

Because replicative HBV infection is associated with an increased risk of chronic hepatitis, hepatic cirrhosis, liver failure, and hepatocellular carcinoma, antiviral therapy has become an important intervention in preventing or slowing the progression of HBV-associated liver disease. Lamivudine, which was given to the patient under discussion, is a nucleoside analogue that is one of four regimens approved by the Food and Drug Administration (along with interferon alfa, adefovir, and entecavir) for treating replicative HBV disease. This drug improves histopathological findings in the liver and the structure of liver tissue, increases the rate

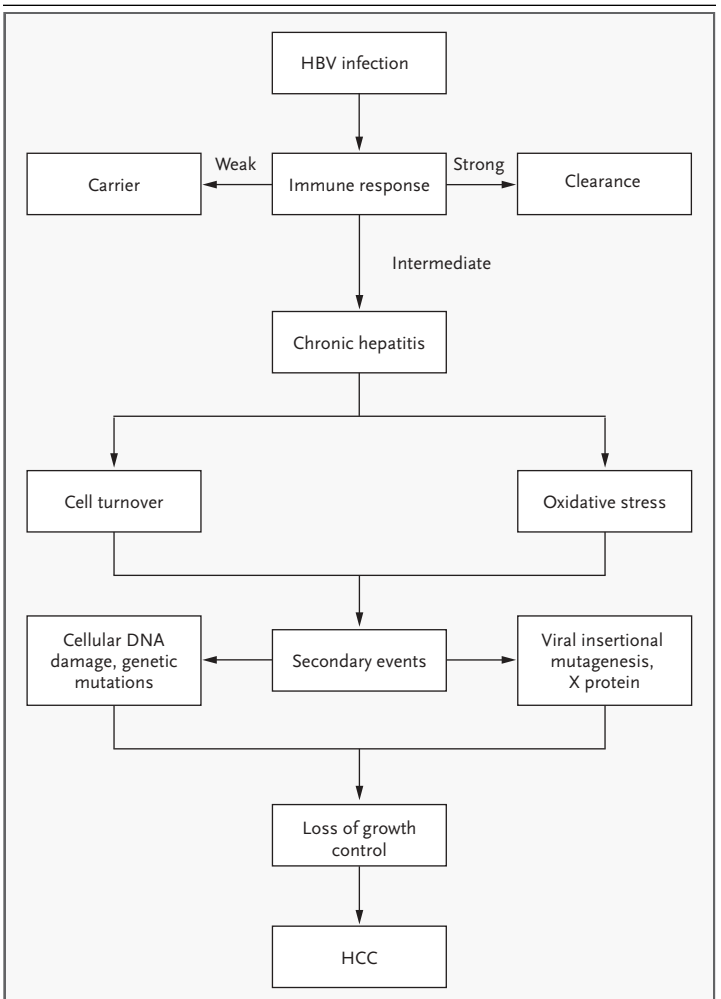


Figure 2. Schematic Representation of the Development of Hepatocarcinogenesis in Association with HBV.

After acute infection with HBV, the paucity of a cytolytic immune response (as is seen in perinatally acquired infection) leads to the inactive carrier state. In contrast, a vigorous immune response (as is seen in infection acquired in adulthood) is associated with successful viral clearance. Between these two states, chronic hepatitis prevails, in which a nonclearing immune response produces ongoing inflammation, injury, and repair, resulting in an increase in cell turnover and oxidative stress. In this setting, cellular DNA damage, chromosomal abnormalities, and genetic mutations occur. In addition, direct viral effects, including insertional mutagenesis and possible direct effects of the hepatitis B X protein, ultimately result in loss of cell growth control and set the stage for malignant transformation in the form of hepatocellular carcinoma (HCC). The illustration is adapted from Chisari.[4]

of HBeAg seroconversion, and may result in improved hepatic function and a decreased risk of hepatocellular carcinoma.[8]

Because of the increased risk of hepatocellular carcinoma associated with chronic HBV infection, patients such as the man in the case under discussion should undergo surveillance.[9] Although recommendations vary as to frequency, regular screening by means of measurements of serum alpha-fetoprotein and ultrasonography appears to be cost-effective in persons from areas where the infection is endemic[10]; such screening is associated with the detection of tumors at a treatable stage in the majority of cases. This patient was at high risk for hepatocellular carcinoma, and his tumor was detected at a relatively early stage.

The patient in this case did not yet have cirrhosis, but for the many who do, the management of hepatocellular carcinoma poses a special challenge. Hepatocellular carcinoma in the cirrhotic liver may be multifocal, and recurrence rates after curative resections are high. Liver transplantation as a means of removing premalignant tissue is a curative procedure for carefully selected patients with hepatocellular carcinoma who have cirrhotic livers.

PRETREATMENT STAGING OF HEPATOCELLULAR CARCINOMA

Dr. Lawrence S. Blaszkowsky: The stage of most solid tumors can be determined with the use of the American Joint Committee on Cancer Staging System, also known as the tumor–node–metastasis (TNM) system.[11] It was recently modified for hepatocellular carcinoma in recognition of the prognostic importance of vascular invasion, and it distinguishes between major and minor vascular invasion; the latter may not be appreciated on preoperative evaluation. However, the majority of patients with hepatocellular carcinoma have advanced liver disease, and they often die of hepatic failure, rather than from extrahepatic tumor progression. The TNM staging system does not take into account the degree of hepatic dysfunction.

The Okuda Staging System was the first to include factors reflecting hepatic function in addition to tumor characteristics. It categorizes the disease in three stages on the basis of the size of the patient's tumor (greater than vs. less than or equal to 50 percent of the liver volume), levels of total bilirubin (greater than vs. less than or equal to 3 mg per deciliter) and albumin (greater than vs. less than or equal to 3 g per deciliter), and the presence or absence of ascites.[12] Problems in determining the correct stage include the difficulty of accurately estimating the volume of tumor, the fact that the bilirubin level used as a criterion is so high that even those below the cutoff may have severe liver dysfunction, and the failure to integrate vascular invasion into the model. Furthermore, because of improvements in screening and radiographic techniques, many patients are now given a diagnosis with smaller tumors than was the case for the patients used in developing the model, so that more stages are needed to stratify these early tumors according to risk.

The Child–Turcotte–Pugh classification is commonly used by gastroenterologists to characterize the degree of hepatic dysfunction; it represents a composite score for the serum bilirubin level, prothrombin time, albumin level, stage of encephalopathy, and extent of ascites. There are three classes (A, B, C), with A the least sick and C the most sick. There are now several staging systems for hepatocellular carcinoma that take into account important factors from the Child–Turcotte–Pugh system, in addition to tumor-specific prognostic factors.[13-16] Among these systems, the Cancer of the Liver Italian Program (CLIP) score has been validated by several groups and in populations of patients with HBV and hepatitis C virus infections. On the basis of this patient's preoperative evaluation, his CLIP score was 0 on a scale from 0 to 6 (with 0 representing the best prognosis and 6 the poorest). This score corresponds to a median survival of 31 to 69 months.

PRIMARY TREATMENT OF HEPATOCELLULAR CARCINOMA

Dr. Kenneth K. Tanabe: Of the several treatment options available for this patient's hepatocellular carcinoma, liver transplantation has the benefits of simultaneous removal of the primary cancer and replacement of the underlying cirrhotic liver, from which subsequent cancers may arise. Disadvantages include the adverse effects of immune suppression on cancer control and the relative shortage of donor livers, which leads to prolonged waiting times for recipients. The results of liver transplantation are poor for tumors of an advanced stage, but relatively good for tumors that are small and incidentally identified in explanted livers.[17,18]

Because of the long wait for donor organs, more than 20 percent of patients need to consider other treatment options during the waiting period and

do not actually undergo transplantation.[19] In the case of this patient, because of his normal liver function, the wait for a transplant was estimated to be greater than six months. However, his tumor had grown rapidly, from 3 cm to 4.7 cm in diameter over a short interval, and we thought that continued tumor progression while awaiting liver transplantation would soon render him ineligible for transplantation because of the tumor size.

Several strategies have been developed to reduce the number of patients who drop out before liver transplantation because of tumor progression. The availability of a living donor essentially eliminates the issue of waiting times. However, the short-term and long-term risks to the donor are not yet well defined and raise important ethical issues concerning the appropriateness of this strategy.[20] Transcatheter arterial chemoembolization, percutaneous ethanol injection, and radiofrequency ablation have been used in the hope that they may serve as "bridges" to transplantation. The absence of data from prospective, randomized, controlled trials of these bridging treatments precludes a clear understanding as to whether any of these strategies improves the outcome.

Percutaneous ethanol injection and radiofrequency ablation could also be considered primary treatment options for this patient. Percutaneous ethanol injection is associated with survival statistics that approach those for partial hepatectomy in patients with Child–Turcotte–Pugh class A or B cirrhosis and a single tumor.[21] Radiofrequency ablation requires fewer treatments than percutaneous ethanol injection and leads to similar survival rates in studies with relatively short follow-up.[22] Local recurrences after radiofrequency ablation of hepatocellular carcinomas are more common in tumors that are larger than 4 cm in size than in smaller tumors. This patient's tumor was approximately 4.7 cm in diameter, so his chances of recurrence after either of these procedures were high.

Because this patient's tumor straddled the right and left functional lobes of the liver, resection options included either an extended left hepatectomy or an extended right hepatectomy (Fig. 3).[23] The risk of postoperative liver failure after extensive resection is high when there is underlying liver disease, such as the hepatitis in this patient. We therefore opted to perform a central hepatectomy.[24] This operation preserves more of the liver than an extended left or right hepatectomy and thereby reduces the risk of postoperative liver failure. The patient had transient mild hepatic insufficiency after the surgery, but he had recovered enough by the seventh postoperative day to be discharged home.

PATHOLOGICAL DISCUSSION

Dr. Gregory Y. Lauwers: The resected liver specimen contained a well-circumscribed mass measuring 4.5 cm in greatest dimension, with the gross characteristics of a hepatocellular carcinoma. The TNM classification uses a cutoff of 5 cm to stratify hepatocellular carcinomas, and there is a statistically significant difference in overall survival, disease-free survival, and the frequency of intrahepatic and hematogenous metastases, as well as portal-vein thrombosis, in the case of tumors that are larger than 5 cm in diameter, as compared with those that are 5 cm or less.[11,25,26]

The pattern of growth in this tumor was classified as single nodular, or type 1 of the classification of the Liver Cancer Study Group of Japan.[27] Different patterns of growth have been associated with varying risks of intrahepatic and extrahepatic spread.[28] Type 1 nodular cancer is associated with the best prognosis, with only a 20 percent rate of recurrence at two years.[29]

The resection margin was negative, with a clearance of 0.5 cm. The importance of ensuring a wide surgical clearance in resections of hepatocellular carcinoma is controversial. Some reports have shown that a clearance of less than 1 cm is associated with higher rates of intrahepatic recurrence, but other reports have not.[30-32] A critical argument against the usefulness of the 1-cm clearance is the frequent detection of synchronous tumors in the residual liver.

The surrounding parenchyma showed various degrees of fibrosis, but no established cirrhosis. In the short term, despite an initially increased operative risk, patients with cirrhosis who have a good hepatic reserve fare as well as patients who do not have cirrhosis.[33] However, in patients who had survived at least five years after their initial surgery, moderate-to-severe fibrosis in the remnant liver was the most important predictor of higher mortality.[34]

The microscopical examination of the tumor revealed a complete fibrous capsule (Fig. 4A). Encapsulation has not been shown to be a significant prognostic indicator of survival in a large multivariate analysis.[32,34,35] The tumor was formed of compact, thickened plates of hepatocytes (Fig. 4A,

inset). The neoplastic hepatocytes had moderate atypia, and the tumor was classified as histologic grade 2. On the basis of a review of 425 curatively resected hepatocellular carcinomas, it was concluded that tumors of grade 1 (good prognosis) and grades 3 to 4 (poor prognosis) were significant predictors of survival in a multivariate analysis, but that tumors of intermediate grade (grade 2) could have either a good or poor prognosis, depending on the presence or absence of microscopic vascular invasion.[32,36,37] Further evaluation of the specimen from this patient revealed microvascular invasion of a medium-sized vein (Fig. 4B); this was not a surprising finding, since the prevalence of such microvascular invasion is about 50 percent in tumors that measure more than 4 cm.[38]

On the basis of the histologic findings (size, vascular invasion, and limited fibrosis), this tumor was classified as stage 1 T2F0, according to the newly modified American Joint Committee on Cancer classification. Despite the relatively small size of the tumor, the presence of microvascular invasion and the moderate nuclear grade place the patient in a category of patients with a poor prognosis. According to a hepatocellular prognostic index designed in 2002 and based solely on histologic characteristics, the median survival after surgical resection alone of patients with tumors such as this, with microvascular invasion and a moderate nuclear grade, was calculated to be about 2.7 years.[26,35]

Figure 3 (facing page). Anatomy of the Liver and the Implications for Partial Hepatectomy.

Panel A shows the functional anatomy of the liver. The left, middle, and right hepatic veins functionally divide the liver into four sectors, and these are further subdivided based on the portal inflow — into a total of eight segments. Panel B shows the morphologic anatomy, in which the right lobe and left lobe are divided by the falciform ligament and umbilical fissure (not shown). The tumor (tan circle) straddled segments IV and VIII. An extended right hepatectomy would remove segments IV through VIII and an extended left hepatectomy would remove segments II through V and VIII. A central hepatectomy, the surgical removal of individual segments (IV, V, and VIII), would allow for preservation of more liver tissue than either the extended left or extended right hepatectomy and would remove entirely those segments that were at greatest risk for intrahepatic micrometastases.

ADJUVANT TREATMENT

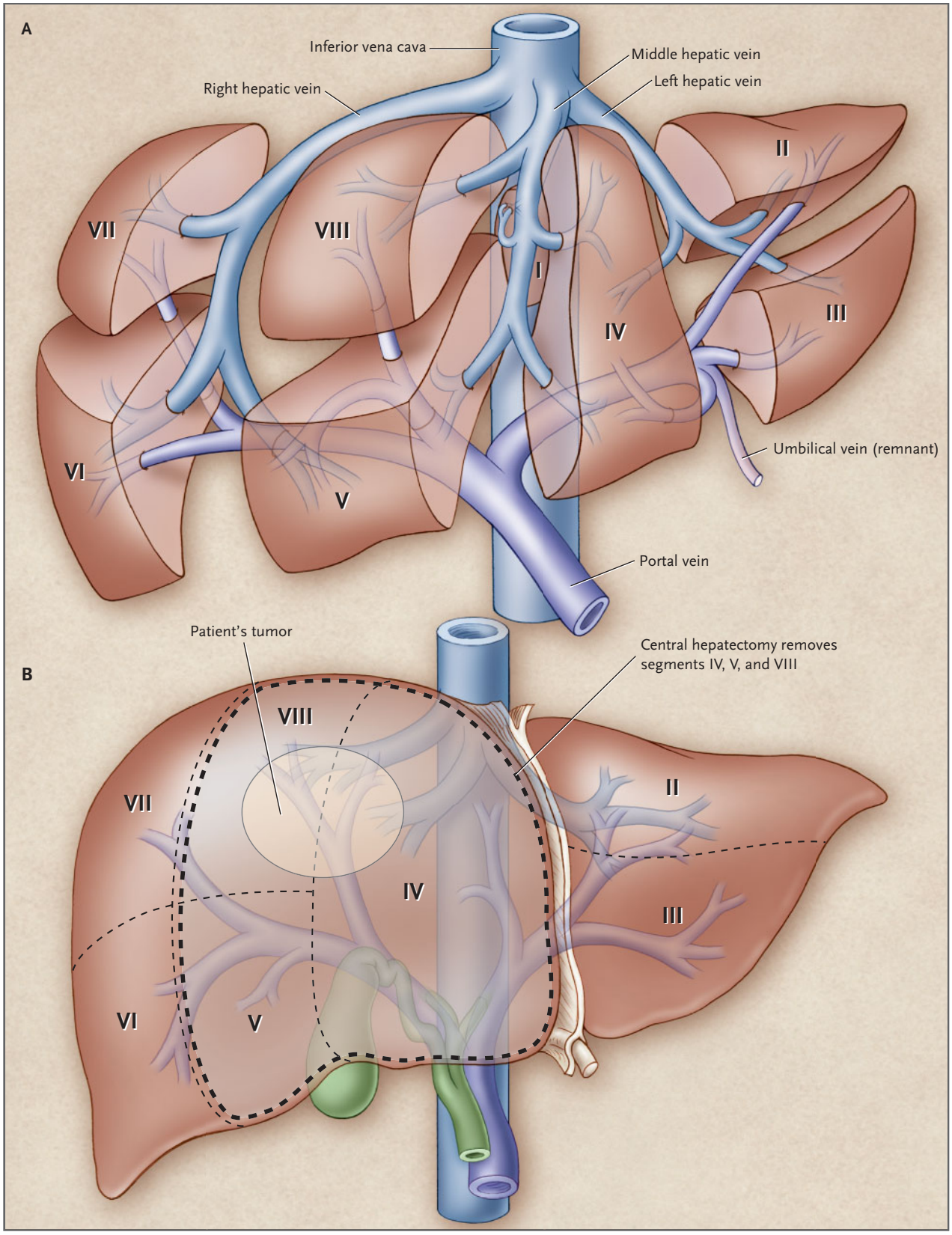
Dr. Tanabe: Since the risk of relapse after primary treatment of hepatocellular carcinoma is high, several adjuvant therapies have been examined in clinical trials. Treatment with transarterial chemoembolization, interferon alfa, interferon beta, and adoptive immunotherapy has been associated with a reduction in the rate of recurrence of tumor in the liver, but not with improved survival, as compared with observation alone. Treatment with both intraarterial iodine-131–labeled ethiodized oil (Lipiodol)[39] and polyprenoic acid, an analogue of vitamin A that inhibits hepatocarcinogenesis in rodents, has produced a reduction in tumor recurrence and an improvement in overall survival, as compared with observation, in randomized clinical trials.[40,41] These agents are not yet available in the United States.

Dr. Blaszkowsky: The patient was not treated with adjuvant therapy after surgery, because of the lack of available effective agents. Eight months after his surgery, a follow-up MRI suggested that there had been a recurrence.

Dr. Blake: Gadolinium-enhanced T_1-weighted images from the follow-up evaluation showed no evidence of local recurrence in the region of the resection site. However, there were new arterially enhancing masses scattered through the liver, which on delayed imaging showed peripheral rim enhancement (Fig. 5, and Fig. 3 of the Supplementary Appendix). These findings are consistent with metastatic disease or multifocal hepatocellular carcinoma.

Dr. Blaszkowsky: Since this patient now had at least eight or nine lesions in his liver, he was not a candidate for transplantation. There are several nonsurgical techniques that were options for this patient: percutaneous ethanol injection, percutaneous thermal ablation, systemic chemotherapy, hormonal therapy, interferon, novel agents, transhepatic arterial chemoembolization, and radiation therapy.

Systemic chemotherapy has had little impact on the course of hepatocellular carcinoma, and rates of response to most agents rarely exceed 10 percent.[42] Hepatocellular carcinomas often express hormone receptors such as estrogen or somatostatin receptors. Seven randomized clinical trials were unable to demonstrate an antitumor effect of treatment with tamoxifen in hepatocellular carcinoma.[43] Although there was no reduction in tumor volume, two of three relatively small, randomized clinical trials evaluating somatostatin analogues showed a statistically significant improvement in survival. There has recently been interest in thalid-



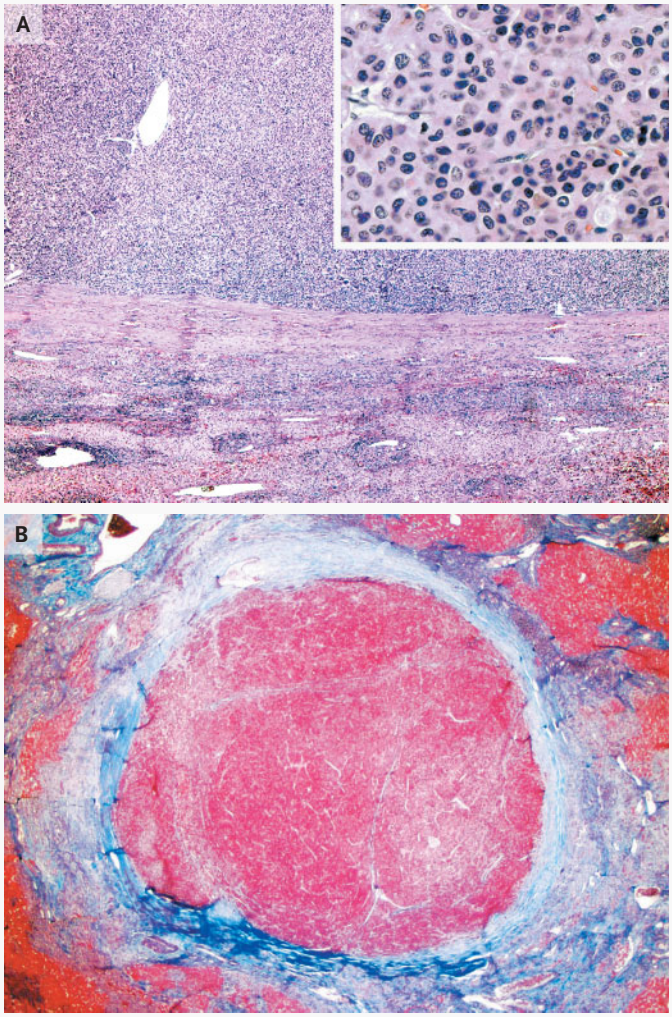


Figure 4. Pathology of the Liver Tumor.

The resected tumor was completely encapsulated (Panel A, hematoxylin and eosin). Microscopical examination revealed a fibrous capsule that was several millimeters thick at the interface. The tumor has a compact macrotrabecular architectural pattern (Panel A, inset). The cytologic features indicate a moderately differentiated hepatocellular carcinoma. Microvascular invasion was identified (Panel B, trichrome stain) in the form of a malignant thrombus that was away from the tumor, in the surrounding hepatic parenchyma.

omide as a therapeutic drug. When it is used as a single agent, response rates are 5 to 7 percent, but in one report of 15 patients treated with thalidomide and capecitabine, the response rate was 18 percent, with 45 percent of the patients having stable disease.[44] Treatment with interferon is minimally active, with considerable toxicity. None of these agents offered the patient under discussion much hope of prolonged survival.

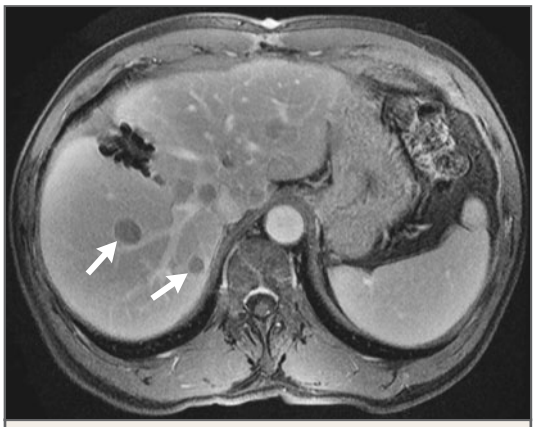


Figure 5. A Follow-up, T_1-Weighted Axial MRI, Obtained after the Administration of Gadolinium.

Eight months after the patient had undergone a partial hepatectomy, an MRI through the liver dome in delayed phase showed several small masses scattered throughout the liver. The masses show delayed peripheral enhancement (arrows) that was consistent with metastases or multifocal hepatocellular carcinoma.

Transhepatic arterial chemoembolization in hepatocellular carcinoma is associated with a response rate of approximately 35 percent. After several randomized clinical trials did not show a statistically significant improvement in survival, two randomized clinical trials did show an improvement in survival of up to two years in patients who received this treatment as compared with those who did not: in one trial, the two-year survival rate was 63 percent, as compared with 27 percent; in the other trial, the two-year survival rate was 31 percent, as compared with 11 percent.[45,46] Use of chemoembolization rather than bland embolization was also associated with a reduction in the development of portal-vein thrombosis. In carefully selected patients, transhepatic arterial chemoembolization may be the most effective treatment currently available. Transhepatic arterial chemoembolization was a reasonable option for this patient; however, he declined the offer of this therapy.

The use of radiation therapy has been limited in hepatocellular carcinoma because of the sensitivity of the liver to radiation. The normal liver can typically tolerate 30 Gy. In selective internal-radiation therapy, yttrium-90–labeled resin-based or glass microspheres are infused into the hepatic artery, resulting in a target dose of 100 Gy to the tumor. One study using this method showed a response rate of 27 percent in 71 patients with unresectable tu-

mors, and 4 of those patients ultimately underwent resection.[47] This therapy is currently not widely available.

Since outcomes with currently available chemotherapeutic agents are disappointing, we offer all patients the option of participation in a clinical trial when available. This patient volunteered to participate in a clinical trial of gemcitabine, oxaliplatin, and the vascular endothelial growth factor–receptor inhibitor bevacizumab, but he had to drop out because of severe nosebleeds that required packing and transfusions. He was then observed for several months, during which he remained asymptomatic. He is now participating in a phase 1–2 clinical trial of a polyamine analogue, N^1,N^{11}-diethylnorspermine. After two months of therapy, CT scans show stable disease in the liver without extrahepatic spread. He remains asymptomatic two years after the partial hepatectomy.

ANATOMICAL DIAGNOSIS

Hepatocellular carcinoma.

Dr. Tanabe reports having received consulting fees from Ethicon Endosurgery. Dr. Blaszkowsky reports holding stock in Pfizer and having received lecture fees from Genentech.

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EDITORIALS

Beta-Blocker Therapy in Noncardiac Surgery

Don Poldermans, M.D., and Eric Boersma, Ph.D.

Perioperative myocardial infarction is a major cause of complications and death among patients undergoing noncardiac surgery.[1] Annually in the United States, approximately 27 million patients are given anesthesia for surgical procedures; of these, approximately 50,000 patients have a perioperative myocardial infarction.[2] The pathophysiology of an acute perioperative myocardial infarction is probably the same as it is for infarction unrelated to surgery.[3] In patients with clinically significant coronary-artery stenosis, myocardial ischemia is induced either by a prolonged mismatch between oxygen demand and supply owing to the stress of surgery or as the result of a sudden rupture of a vulnerable plaque followed by thrombus formation and occlusion.

Beta-blockers are commonly used to correct the imbalance between myocardial oxygen demand and supply. In the late 1980s, indications for beta-blocker therapy were hypertension and coronary artery disease, whereas heart failure and peripheral atherosclerotic disease were considered relative contraindications. However, subsequent research has led to the routine use of beta-blockers in patients with stable heart failure. Beta-blockers are also now recommended for patients with peripheral arterial disease who are undergoing vascular surgery.[4]

Despite recommendations by the American Heart Association–American College of Cardiology for the use of beta-blockers in patients with risk factors for coronary artery disease or proven coronary artery disease who are undergoing any type of high-risk surgery (such as intrathoracic or intraperitoneal procedures), evidence of the efficacy of this approach from randomized clinical trials is limited. In a placebo-controlled trial involving 200 high-risk patients, Mangano et al. found that atenolol (50 or 100 mg), administered intravenously beginning 30 minutes before surgery and then orally throughout hospitalization, did not lower the risk of death from cardiac causes or myocardial infarction during hospitalization.[5] However, it did result in a 50 percent reduction in myocardial ischemia, as assessed by continuous 48-hour Holter monitoring. The DECREASE study (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography), involving a high-risk population of 112 patients who were undergoing vascular surgery, showed that the rate of perioperative death from cardiac causes and myocardial infarction among patients who were randomly assigned to bisoprolol therapy (5 or 10 mg) started at least 30 days before surgery was 90 percent lower than that among patients assigned to standard care (3.4 percent vs. 34 percent).[6] In a meta-analysis of six randomized trials involving 694 surgical patients, beta-blockers were associated with a 75 percent reduction in the risk of perioperative death from cardiac causes.[7]

However, not all studies have reported favorable results for beta-blockers. The recently completed DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, involving 921 patients with diabetes who were undergoing noncardiac surgery, failed to show that metoprolol significantly decreased the risk of death and cardiac complications.[8]

In this issue of the *Journal*, Lindenauer et al. report the results of a very large observational study assessing the association between the perioperative use of beta-blockers and in-hospital mortality.[9] The study compared outcomes among 119,632 patients who received beta-blockers during a surgical admission with outcomes among an even greater number of patients who did not receive beta-blockers and who were matched according to the Revised Cardiac Risk Index (RCRI) score. This index stratifies the risk of perioperative cardiac events according to the type of surgery and the presence or absence of a

history of ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative treatment with insulin, and a preoperative serum creatinine level greater than 2.0 mg per deciliter (176.8 μmol per liter).[10] Scores can range from 0 to 5, and the likelihood of major perioperative complications increases with increasing scores. A patient was considered to have used a beta-blocker if such a medication was prescribed during the first two days after admission. Follow-up was restricted to the period of hospitalization. Overall, beta-blocker use was not associated with a reduced risk of death. However, a steep gradient in the treatment effect was observed in relation to the RCRI score. Beta-blocker use was associated with a 43 percent increase in the risk of death among patients with an RCRI score of 0 and a 13 percent increase among patients with a score of 1; in contrast, it was associated with a reduction in the risk of death (ranging from 10 percent to 43 percent) among patients with a score of 2, 3, or 4 or greater. Thus, beta-blockers appeared to be harmful in low-risk patients, neutral in patients at intermediate risk, and beneficial in high-risk patients.

Previous reports have suggested that the absolute reduction in risk associated with beta-blocker use is most pronounced in patients at high risk for coronary events.[11] However, an interaction between beta-blockers and cardiovascular risk factors, as found by Lindenauer et al., has not previously been observed. In fact, it is hard to explain why beta-blockers would not confer protection in patients with a limited number of risk factors — for example, only a history of ischemic heart disease — but would do so if one or two additional risk factors were present, such as diabetes mellitus or renal dysfunction. As the authors acknowledge, it is possible that the approach they used to identify patients taking beta-blockers was at least partially responsible for this unexpected observation. Beta-blockers may have been given to many low-risk patients in response to a cardiovascular complication, rather than to prevent one. The lack of information in the database on the timing of prescriptions for beta-blockers relative to surgery or on indications for prescribing made it impossible for the authors to address this issue.

How might beta-blockers improve the postoperative outcome among high-risk patients? Beta-blockers prolong coronary diastolic filling time and may prevent fatal ventricular arrhythmias and the rupture of atheromatous plaque in the presence of high sympathetic nervous system drive.[4] These effects may vary with the dose and type of beta-blocker (cardioselective vs. nonselective), as well as with the associated degree of heart-rate control. A small randomized study showed a reduced incidence of myocardial ischemia among patients assigned perioperatively to a regimen that tightly controlled the heart rate (to a maximum of 80 percent of the heart rate at which ischemia had been detected before surgery during ambulatory electrocardiographic monitoring), as compared with those assigned to usual care.[12] Also, all cardiac risk factors may not be equal. For instance, a history of repeated episodes of myocardial ischemia may render the heart more resistant to damage from a prolonged ischemic insult and thus reduce the likelihood or size of a perioperative infarction.[13] Data on such factors are lacking in the study by Lindenauer et al., and therefore beta-blockers may have had differential effects in high-risk as compared with low-risk patients.

The apparent beneficial effect of beta-blockers in high-risk surgical patients in the present study, coupled with earlier reports of such benefits in small randomized trials, supports the routine use of beta-blockers in high-risk patients undergoing noncardiac surgery. Two ongoing randomized trials may help clarify the role of beta-blockers in low-risk or intermediate-risk patients.[14,15] The POISE (Perioperative Ischemic Evaluation) study is designed to evaluate the ability of metoprolol to prevent death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal cardiac arrest in 10,000 patients undergoing all types of noncardiac surgery. DECREASE-IV is designed to evaluate the efficacy of combination therapy with fluvastatin and bisoprolol in 6000 patients scheduled to undergo noncardiac, nonvascular surgery, excluding minor surgery. Pending the availability of data from these trials (expected within four years), we believe it is appropriate to continue beta-blocker therapy in patients at low or intermediate risk, given the potential cardiac risks associated with the sudden interruption of beta-blocker therapy. Further information is needed before the perioperative use of beta-blockers should be considered routinely in other patients at low or intermediate risk.

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Progressive Multifocal Leukoencephalopathy and Natalizumab — Unforeseen Consequences

Joseph R. Berger, M.D., and Igor J. Koralnik, M.D.

In this issue of the *Journal*, there are reports describing in detail three patients in whom progressive multifocal leukoencephalopathy (PML) developed during treatment with natalizumab, a humanized monoclonal antibody against α_4 integrins.[1-3] These patients were among 3000 who had participated in clinical trials of natalizumab for the treatment of multiple sclerosis or Crohn's disease. PML is a deadly opportunistic infection of the central nervous system (CNS) for which there is no specific treatment. It is caused by reactivation of a clinically latent JC polyomavirus infection. This virus infects and destroys oligodendrocytes, leading to multifocal areas of demyelination and associated neurologic dysfunction. The occurrence of PML in this setting was totally unexpected, since it almost invariably occurs in the context of profoundly impaired cell-mediated immunity in patients with AIDS or leukemia or in organ-transplant recipients.

In retrospect, can we retrace the events that led to the surprising development of PML in these three patients? Seropositivity rates for JC virus, the etiologic agent of PML, increase with age and vary in different populations. After infection, the virus remains quiescent in the kidneys and in lymphoid organs of people with immunocompetence. The virus is often present in the urine but is generally not found in the blood. However, JC viremia can be detected in persons with immunosuppression, and hematogenous dissemination is the likely route of entry into the CNS.[4]

Since the authors of the present reports did not provide data on the serologic status of JC virus for the patients, we can only assume that the patients had been infected in childhood. If this is the case, what role did the multiple medications taken by these persons play in the reactivation of JC virus, which eventually led to PML? Retrospective analysis of serum samples that were obtained between 1999 and 2003 from the patient with Crohn's disease provides an important answer: JC virus became detectable only in May 2003, after three injections of natalizumab monotherapy, two months before the patient was admitted to the hospital. Moreover, the serum viral load increased by a factor of 10 after two additional injections.

Therefore, it appears likely that natalizumab, by preventing normal trafficking of lymphocytes, led to unbridled JC virus replication in this patient. Consistent with this scenario, inflammatory infiltrates were conspicuously absent from the brain lesions. Indeed, the cellular immune response, principally mediated by CD8+ cytotoxic T lymphocytes,

has been shown to play a major role in the containment of JC virus.[5,6] In the patients with multiple sclerosis, the presence of JC viremia was not tested retrospectively before the onset of neurologic symptoms of PML, and the role of the concomitant administration of interferon beta-1a in JC virus reactivation remains unknown. However, PML has not been reported previously in association with this disease-modifying agent for multiple sclerosis.

If impaired immune surveillance due to treatment was responsible for the development of PML, from what site or sites did the virus reactivate? The lack of analysis of urine and kidney or lymphoid tissues precludes comment on whether these organs were the epicenter of JC virus dissemination in the body.

Could the virus have already been present in a latent stage in the brain, or did it reactivate from multiple sites? There are conflicting reports in regard to the detection of JC virus in the CNS and the digestive systems of persons with immunocompetence, and this issue is still unsettled. In the patient with Crohn's disease, however, intestinal samples obtained three years before the development of PML showed no JC virus DNA. In any event, the development of PML in these three patients — in whom the entry of mononuclear cells into the brain, at least in theory, should have been significantly diminished or entirely blocked — suggests that JC virus may enter by other means, perhaps as free virus.

What can we learn from the clinical course of these patients' illnesses? Certain elements of the cases are worthy of comment. Arriving at a diagnosis of PML may be challenging, and mistaking PML for a primary brain tumor or a stroke may occur on occasion. However, the imaging findings of a multifocal process that is limited to the white matter and that exhibits neither mass effect nor enhancement with contrast material should always raise the suspicion of PML. In the absence of a contraindication to lumbar puncture, the demonstration of a positive result on polymerase chain reaction (PCR) for JC virus in the cerebrospinal fluid establishes the diagnosis when coupled with the appropriate clinical and radiologic features.

The classic histopathologic hallmarks of PML include enlarged oligodendroglial nuclei at the border of areas of demyelination; giant, bizarre astrocytes; and lipid-laden macrophages that scavenge myelin debris. In situ hybridization or immunohistochemical staining permits identification of the virus. The pathological findings in one of the patients with multiple sclerosis[1] of massive, coalescent areas of cavitation of the brain are atypical, although not unheard of, in PML.

Since treatment with natalizumab was eventually discontinued in the three patients, how can we explain the differences in their clinical outcomes? In patients with AIDS who have PML and are treated with highly active antiretroviral therapy, recovery of the immune system is associated with increased long-term survival (i.e., more than one year), from just under 10 percent[7] to approximately 50 percent.[8] One may therefore wonder why the two patients who died four[1] and five[3] months after the time of presentation did not stabilize or recover once natalizumab administration had been stopped. By binding to the surface of lymphocytes and monocytes, natalizumab prevents the passage of these cells from the bloodstream into the parenchyma of various organs. Perhaps the fact that as many as 80 percent of the α_4-integrin receptors of peripheral blood lymphocytes remain saturated one month after infusion[9] explains this continuing process, and a biologic effect may be observed up to three months after the administration of natalizumab.[10]

Consistent with this hypothesis, approximately three months after discontinuing natalizumab, the surviving patient with multiple sclerosis presented with an immune-reconstitution inflammatory syndrome,[11] which was probably caused by the return of lymphocytes to the CNS and was characterized by contrast enhancement of PML lesions. This inflammatory reaction was associated with a decreased JC viral load in the blood and cerebrospinal fluid as well as transient worsening followed by neurologic improvement. This patient was also the only one who received medications other than corticosteroids, including intravenous immune globulin, cidofovir, and cytarabine. Of these, only cytarabine has been demonstrated to have activity against JC virus in vitro. It is interesting that the breakdown of the blood–brain barrier in this patient was probably instrumental in increasing the intraparenchymal distribution of this drug, which has limited efficacy in the treatment of PML[12,13] due to poor penetration into the CNS.[14] Furthermore, the incidental finding of an asymptomatic PML lesion on magnetic resonance imaging may have led to earlier intervention in this patient's clinical course, as compared with the patients who died from PML. In the latter patients, the disease was probably too advanced once the effect of natalizumab wore off to

be contained by lymphocytes capable of returning to the brain parenchyma.

Would it be possible to predict and prevent the occurrence of PML in patients receiving α_4-integrin blockers? Only persons infected with JC virus are at risk for PML, but the rate of seropositivity for this virus is from 50 to 86 percent in healthy adults.[15,16] This is probably explained in part by differences in the sensitivity of the assays used and underscores the need for a highly sensitive, universally accepted enzyme-linked immunosorbent assay.

If past serum samples are available, retrospective measurement by quantified PCR of the JC viral load in the plasma of patients with Crohn's disease and multiple sclerosis who were treated with natalizumab will be necessary to determine the predictive value of this test for the development of PML in patients with these conditions. This information will probably be equally important with regard to other biologic agents or medications that inhibit lymphocyte migration. The data acquired from such a retrospective analysis would be essential to determine whether it will be possible to fashion preventive strategies against the development of PML in patients treated with natalizumab or similar drugs in the future.

The prospective measurement of the JC viral load in plasma and the preemptive reduction of doses or interruption of treatment if JC virus DNA appears in the blood might actually prevent the development of PML in this setting. By analogy, a similar strategy has been used successfully for the prevention of a nephropathy caused by the JC virus-related BK polyomavirus in kidney-transplant recipients.[17] In addition, analysis of the JC virus regulatory region, which contains determinants of neurotropism and neurovirulence,[18] may provide important insight into the mechanisms of JC virus reactivation in patients treated with novel immunomodulatory medications.

Finally, these observations provide a unique and unexpected window into our understanding of the pathogenesis of PML and force us to reconsider the potential risks associated with inhibition of lymphocyte trafficking. Bad things may happen when rescuers are turned back at the gates.

Dr. Berger reports having received consulting or lecture fees from Berlex, Biogen Idec, Elan, and Serono and grant support from Berlex; and Dr. Koralnik, consulting fees from Berlex and Biogen Idec.

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This editorial was published on June 9, 2005, at www.nejm.org.

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Patients at Risk

Jeffrey M. Drazen, M.D.

In clinical trials, the term "patients at risk" refers to the altruistic people who volunteer to participate in studies of novel treatments. In this issue of the *Journal*, three reports[1-3] provide details about patients who were participating in trials involving experimental treatment with natalizumab for either multiple sclerosis or Crohn's disease and who were affected by progressive multifocal leukoencephalopathy (PML). PML is a rapidly progressive, often fatal demyelinating brain disorder caused by infection of the central nervous system with JC virus[4]; it usually occurs in patients with diminished T-cell function. These events remind us once again of the true meaning of being a "patient at risk."

The clinical story is intriguing. Natalizumab (Tysabri) is a humanized monoclonal antibody to the T-cell adhesion molecule known as α_4 integrin; patients given the antibody have suppressed T-cell function. The agent was approved by the Food and Drug Administration for the treatment of multiple sclerosis in November 2004, but the manufacturer, Biogen Idec, has been conducting continuing clinical tests with the agent to clarify its role in the treatment of a number of medical conditions. In February of this year, two cases of PML in patients with multiple sclerosis were diagnosed among those at risk in these ongoing trials. Biogen Idec then put a halt to the sales and testing of the drug. In this issue of the *Journal*, Kleinschmidt-DeMasters and Tyler[1] and Langer-Gould et al.[2] provide the medical details of these cases of PML in patients with multiple sclerosis.

Once they were on high alert, investigators in Belgium revisited a case of what had originally been considered to be a fatal astrocytoma in a patient participating in a clinical trial of natalizumab for the treatment of Crohn's disease. As detailed by Van Assche and colleagues,[3] they quickly discovered that the patient had actually died from PML. These investigators provide strong evidence, based on a detailed chronology of recovery of JC virus from the blood, of a temporal association between treatment with natalizumab and PML.

Given these data, the association between treatment with natalizumab and the occurrence of PML seems clear. What we do not know is the magnitude of the risk of PML per year of exposure. It is our understanding that Biogen Idec has examined as many of the patients who received the drug as possible for evidence of virus in the blood or for imaging findings consistent with PML to determine whether there is a reservoir of subclinical cases. Here is where close surveillance for further active or subclinical cases of PML becomes so important. These data are needed to set provisional bounds on the risk of acquiring PML. With this knowledge, a reasonable assessment of the risk of this complication versus the treatment benefit can be made. In the case of natalizumab, there is a dilemma. On the one hand, it appears to be a promising therapy for multiple sclerosis and has raised the hopes of patients with this debilitating condition; on the other, the complication of PML can be fatal.

The bottom line is sobering. If we are to advance the art of medicine, we need patients who are willing to volunteer to be subjects in clinical trials. Despite the obstacles presented by adverse outcomes, clinical research must proceed if new therapies are to be developed. We always need to remember that these patients are "at risk." We need to be sure that research is carried out in a responsible manner and that patients who volunteer to participate are treated in an open, honest, and fair fashion; from what is currently on the public record, Biogen appears to have honored this trust. Patients and their families expect no less, and we must always deliver on that expectation.

This editorial was published on June 9, 2005, at www.nejm.org.

1. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005; 353:369-74.

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Insurance and the U.S. Health Care System

Barbara Starfield, M.D., M.P.H.

Nearly 15 percent of children in the United States are inadequately insured because they lack health insurance for all or part of the year. In this issue of the *Journal*, Olson and colleagues[1] describe the potent effect of inadequate insurance coverage on several aspects of access to services. They also examine several other effects of inadequate insurance coverage. Olson et al. characterized insurance coverage as full-year, part-year, or none and as private or public. The manifestations of compromised access to services were delays in seeking care, unmet medical care needs, unfilled prescriptions, no visits to doctors' offices, the lack of usual places for care, and no well-child visits.

Hispanic children were by far the most likely to be inadequately insured. Inadequate insurance coverage was associated with all manifestations of compromised access to services. Another notable finding was that public insurance was associated with better receipt of well-child care and physicians' services than was private insurance for children in poor health.

Although having health insurance coverage is related to the use of health care services and enables people to have a consistent source of care,[2,3] we cannot be sure that having insurance guarantees the receipt of high-quality care, particularly for children who are at a disadvantage because of their social class or race or ethnic group. Such children are likely to receive their care in hospital outpatient clinics and emergency rooms[4,5] — facilities that generally are not designed to provide strong primary care.

In considering the possible confounding effects of family income, race or ethnic group, family structure, parental employment, geographic region, and citizenship on the health care coverage of children, the authors examined each while holding constant the influence of the others. Some of the findings in these analyses were unexpected and require closer examination.

When the level of insurance coverage and other possible confounders were controlled, children who were citizens of the United States were more likely than children who were not citizens to have delayed care, unmet medical care needs, or unfilled prescriptions but less likely to lack usual places for care, to have no well-child visits, or to have no visits to doctors' offices. Hispanic children were less likely than non-Hispanic blacks, whites, or others to have delayed care and no well-child visits but more likely to lack usual places for care and to have no visits to doctors' offices. Non-Hispanic black children were not disadvantaged in any of these ways except for being more likely to have no visits to doctors' offices. These aspects of access would be expected to be the same in their associations with sociodemographic characteristics, but they are not. Are there other characteristics of the health care system that act as powerful mediators in different areas, for providers of different types, and across populations with distinct characteristics?

Only two characteristics were consistently and independently related to all manifestations of compromised access to services. These were being uninsured (especially all year) and being poor. Family structure and parental employment had no relationship with any of the manifestations of compromised access. Race or ethnic group, citizenship status, and geographic region had inconsistent relationships with the manifestations of compromised access, which suggests that there may be unexamined interactions or perhaps even important characteristics of the health care system (other than insurance) that were not included in the analysis.

Two merging areas of focus in the medical care literature suggest possible explanations for these inconsistencies. Researchers at Dartmouth Medical School have demonstrated large variations in the use and costs of services among geographic areas that are unrelated to a better quality of care or better outcomes.[6,7] Although the research is based on Medicare populations, there is no reason to expect anything different for children, according to similarities between adults and children in studies of hospitalizations.[8]

The second area of focus concerns the benefits of good primary care, defined as high levels of first-contact accessibility, patient-focused care over time, a comprehensive package of services, and coordination of services when services have to be provided elsewhere.[9] Studies have shown the beneficial effect of primary care on a myriad of health outcomes, both in adults and in children. Rates of low birth

weight among infants; infant mortality; total mortality; and mortality from heart disease, cancer, and stroke are lower and outcomes such as life expectancy and receipt of preventive care are better in areas with higher ratios of primary care physicians to population, in populations that receive their ongoing care in a primary care facility or from a primary care practitioner, or in populations whose primary care is of high quality as measured by objective criteria.[10,11]

Beyond the association between insurance and access, the findings of Olson et al. provide no clues about how having health insurance coverage might improve the health of children. Only one variable in the study concerns an aspect of care specifically related to health status: receiving well-child care. The "usual places for care" variable was treated as an outcome, although it is a known link in the chain of insurance, appropriate care, and improved health outcomes. It is likely that access to different types of "usual places for care" would have notable effects on the appropriateness of care and health outcomes. Unfortunately, the type of usual place for care was not considered in the analysis, which combined all types of places in one category.

On ethical grounds alone, it is unconscionable that the United States is the only industrialized country to lack universal financial coverage for health services. But the United States is an outlier in other ways that influence health, most particularly in the absence of a strong focus on primary care services.[12] Given the wide confidence intervals for many of the characteristics and persisting disparities when the presence of insurance is accounted for, it may be that insurance coverage alone (and especially private insurance) will not be enough to reverse the consistent disadvantages that low-income children have. Expansions of private insurance coverage may even magnify current problems, such as the multiplicity of insurance policies and benefit structures, the administrative expenses that increase the costs of the U.S. health care system,[13] and the receipt of care from sources that are unable to minimize excessive, unnecessary, and inappropriate specialty services. Without strong efforts to avoid exacerbating administrative waste and the receipt of care from inappropriate services, we cannot be sure that expansions of insurance coverage alone will live up to expectations for improving health.

Olson and colleagues have provided the basis for thinking more logically about the role that health policy must play in improving the health of children in the United States — which has been declining relative to the health of children in other industrialized nations.[14] Insurance coverage is only one means to the end of providing effective and equitable health care services. We know that appropriate health care services improve health and reduce disparities in health across population groups. The country needs universal financial coverage for health care services, but it also needs a delivery system that ensures a source of good primary care and minimizes inappropriate services. Our efforts to influence health policy should focus not only on improving access but also on determining what insurance coverage should accomplish in improving and paying for health care services.

From Johns Hopkins University, Baltimore.

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CORRESPONDENCE

Effectiveness of Antimalarial Drugs

TO THE EDITOR: In his review article (April 14 issue), Baird[1] states that prescribing "chloroquine . . . in any setting, except one in which its effectiveness has recently been demonstrated, should be considered irresponsible." As physicians who have worked in rural Zambia, where malaria is endemic, we have witnessed the effect of falciparum malaria on children and are sensitive to Baird's concerns. However, adults rarely become severely ill. We think that chloroquine remains an inexpensive, rapid-acting drug with few side effects and that it is effective in most patients.

However, recent policy changes removed chloroquine from our formulary on short notice and without an effective and timely alternative. When artemether-based drugs were supplied, the cost, which was 20 to 50 times that of chloroquine, prevented its full implementation or use in patients for whom it was clearly indicated. In addition, the removal of chloroquine made its use in combination with sulfadoxine–pyrimethamine impossible, thereby eliminating an effective treatment and increasing the chance of the development of resistance to sulfadoxine–pyrimethamine.[2]

We believe that chloroquine continues to have a useful role in regions where falciparum malaria is endemic and resources are severely limited, even in the face of significant resistance.

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TO THE EDITOR: The adapted map in Figure 1 and its legend in Baird's article are misleading and appear to suggest that the southernmost African countries — South Africa, Swaziland, Lesotho, Botswana, and Namibia — have no malaria. Although these countries have some of the lowest rates of malaria in southern Africa (overall rate, <0.1 person at risk per square kilometer), malaria remains a major cause of disease, death, and poverty there. Despite the presence of malaria-free districts, 10 percent of the people in South Africa and 66 percent of those in Namibia reside in regions with malaria that have stable or unstable (epidemic-prone) transmission of malaria.[1] The resistance of *Plasmodium falciparum* (the main plasmodium parasite) to chloroquine is widespread, resistance to sulfadoxine–pyrimethamine is becoming increasingly common, and multidrug resistance has been reported.[2-4] In these countries with unstable malaria transmission, all age groups are at risk for

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malaria, whereas in the southern African countries with stable malaria transmission (Angola, Comoros, Madagascar, Malawi, Mozambique, Tanzania, and Zambia), children younger than five years of age and pregnant women are at the greatest risk for malaria.

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TO THE EDITOR: Baird states that "mefloquine given as prophylaxis is as well tolerated as other antimalarial drugs." Recent trials do not support this view, however. Three randomized, controlled trials of mefloquine prophylaxis in nonmilitary travelers reported an excess of adverse neuropsychiatric effects in the mefloquine groups.[1-3] Schlagenhauf and colleagues noted that mefloquine and chloroquine–chloroguanide were associated with similar rates of adverse events and that both regimens showed a trend toward a greater frequency of severe adverse events than did regimens of doxycycline or atovaquone–chloroguanide (12 percent had adverse events with chloroquine–chloroguanide and 11 percent with mefloquine, vs. 7 percent with atovaquone–chloroguanide and 6 percent with doxycycline; P=0.14); the frequency of mild-to-moderate adverse effects showed a similar pattern (P=0.05, for the comparison of all four treatments).[3]

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The recent studies cited by Croft et al. were discussed in my review. We have differences of interpretation. Croft et al. express the view that mefloquine should no longer be used as first-line prophylaxis on the basis of what I consider statistically insignificant (P=0.14) differences in the risk of severe adverse events between this and other antimalarial drugs. On the less important issue of mild-to-moderate adverse events, mefloquine and

chloroquine–chloroguanide (a drug combination used successfully by travelers for several decades but now abandoned because of poor protective efficacy) are similar. On the basis of adverse-event profiles, mefloquine clearly is associated with a statistically significant higher risk of neuropsychiatric symptoms than other antimalarial drugs, as I explained in my review. For most travelers who are considered good candidates for mefloquine prophylaxis, including pregnant women and young children, the regimen carries distinct advantages in terms of cost, convenience, proven efficacy, and demonstrated safety. The suggestion that the safety and adverse-event profiles of mefloquine hinge on very early and limited clinical trials in special populations may mislead readers; mefloquine has been widely used by the traveling public for more than a decade. The responsibility for the decision to recommend mefloquine as first-line or as alternative prophylaxis rests with the national authorities weighing factors of safety, efficacy, cost, and other determinants of effectiveness in the context of the populations they serve.

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Respiratory Syncytial Virus Infection in Elderly Adults

TO THE EDITOR: Falsey et al. (April 28 issue), in their report on respiratory syncytial virus (RSV) infection in elderly and high-risk adults,[1] claim that "the symptoms and signs of RSV infection and those of influenza were not substantially different" and also that the demographic and clinical characteristics of the patients with influenza and of those with RSV infection were similar. If the clinical manifestations of the two diseases were the same, and if the populations that were affected could not be distinguished, how do the authors explain the striking differences between the patients with influenza and those with RSV infection in the rate of office visits (42 percent vs. 17 percent, respectively) and use of antibiotics (33 percent vs. 9 percent)?

Most clinicians make treatment decisions on the basis of a combination of science, experience, and intuition. I suspect that there was some difference that was either not captured or not quantified that influenced both patients' decisions to see a physician and physicians' decisions to prescribe an antibiotic.

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1. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infections in elderly and high-risk adults. N Engl J Med 2005;352:1749-59.

TO THE EDITOR: Falsey and colleagues probably underestimate the burden of influenza-related mortality among elderly patients. Influenza-related hospitalization often results from secondary bacterial infection that occurs after the virus is cleared, hampering confirmation of the presence of the virus by viral isolation, polymerase-chain-reaction analysis, or serologic studies on admission. Studies of excess mortality,[1,2] which sidestep the difficulties of case ascertainment, set the current mortality burden associated with influenza in the elderly at three times that of RSV infection.

This point pales, however, beside the fascinating data presented by Falsey et al. on the benefits of influenza vaccine. Vaccine coverage among elderly hospitalized patients with confirmed influenza was 68 percent, as compared with 75 percent among those with RSV infection, indicating that the efficacy of vaccination in preventing influenza-related hospitalizations was only 29 percent (95 percent confidence interval, 2 to 48 percent). A single clinical trial of influenza vaccination in the elderly showed that the efficacy of the vaccine against mild influenza was 57 percent.[3] Cohort studies without laboratory confirmation show an astonishing benefit in terms of mortality from all causes in the elderly, but such studies are prone to self-selection bias and overestimation.[2,4] We think the study by Falsey et al. may come closest to the truth for severe

CORRESPONDENCE

Effectiveness of Antimalarial Drugs

TO THE EDITOR: In his review article (April 14 issue), Baird[1] states that prescribing "chloroquine . . . in any setting, except one in which its effectiveness has recently been demonstrated, should be considered irresponsible." As physicians who have worked in rural Zambia, where malaria is endemic, we have witnessed the effect of falciparum malaria on children and are sensitive to Baird's concerns. However, adults rarely become severely ill. We think that chloroquine remains an inexpensive, rapid-acting drug with few side effects and that it is effective in most patients.

However, recent policy changes removed chloroquine from our formulary on short notice and without an effective and timely alternative. When artemether-based drugs were supplied, the cost, which was 20 to 50 times that of chloroquine, prevented its full implementation or use in patients for whom it was clearly indicated. In addition, the removal of chloroquine made its use in combination with sulfadoxine–pyrimethamine impossible, thereby eliminating an effective treatment and increasing the chance of the development of resistance to sulfadoxine–pyrimethamine.[2]

We believe that chloroquine continues to have a useful role in regions where falciparum malaria is endemic and resources are severely limited, even in the face of significant resistance.

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TO THE EDITOR: The adapted map in Figure 1 and its legend in Baird's article are misleading and appear to suggest that the southernmost African countries — South Africa, Swaziland, Lesotho, Botswana, and Namibia — have no malaria. Although these countries have some of the lowest rates of malaria in southern Africa (overall rate, <0.1 person at risk per square kilometer), malaria remains a major cause of disease, death, and poverty there. Despite the presence of malaria-free districts, 10 percent of the people in South Africa and 66 percent of those in Namibia reside in regions with malaria that have stable or unstable (epidemic-prone) transmission of malaria.[1] The resistance of *Plasmodium falciparum* (the main plasmodium parasite) to chloroquine is widespread, resistance to sulfadoxine–pyrimethamine is becoming increasingly common, and multidrug resistance has been reported.[2-4] In these countries with unstable malaria transmission, all age groups are at risk for

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malaria, whereas in the southern African countries with stable malaria transmission (Angola, Comoros, Madagascar, Malawi, Mozambique, Tanzania, and Zambia), children younger than five years of age and pregnant women are at the greatest risk for malaria.

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outcomes because it analyzed influenza-specific hospitalizations, and the presence of elderly controls who were hospitalized with RSV infection eliminated self-selection bias. We agree wholeheartedly with Falsey et al. that better vaccine formulations for the elderly are needed.

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THE AUTHORS REPLY: Gorelick suggests that the clinical characteristics of influenza and RSV infection were probably different since significantly greater numbers of otherwise healthy elderly patients with influenza visited a physician and were prescribed antibiotics. We and other investigators have noted that the presence of fever and gastrointestinal symptoms are more common with influenza, whereas rhinorrhea and wheezing are more common with RSV infection.[1-4] However, the degree of overlap limits the usefulness of signs and symptoms for clinical diagnosis in individual patients. Furthermore, these clinical differences become increasingly blurred in high-risk groups. Clearly, healthy, elderly patients infected with influenza virus felt worse than those with RSV infection, as evidenced by the acute functional effect we observed. However, the only significant difference was the presence of dyspnea (25 percent among those with influenza vs. 5 percent among those with RSV infection, P=0.05). We understand the need for busy practitioners to make treatment decisions on the basis of clinical grounds, but we maintain that everything that looks like "the flu" in the winter is not. Rapid, sensitive, and specific viral diagnostic tests might help augment intuition.

We agree with Simonsen and Viboud that influenza-related mortality may have been underestimated in our study. Although serologic studies may identify influenza in some patients hospitalized with secondary bacterial infections, those with rapidly rising antibody titers would certainly be missed. In addition, influenza epidemics have been associated with peaks in cardiovascular and cerebrovascular events, and influenza-related hospitalizations due to these diagnoses would not have been captured in our study.[5] However, the same may also hold true for RSV infection, especially with regard to secondary bacterial infections. Our data indicate that 10 percent of patients with RSV infection and 7 percent of patients with influenza A had mixed viral–bacterial infections at the time of hospitalization.

With regard to the efficacy of influenza vaccine, we caution readers that our study was not designed to evaluate vaccine efficacy. We agree that the patients with RSV infection constitute an excellent control group; however, the vaccination status of each patient was ascertained by interview but not confirmed. In addition, during two of the four years of study, the availability of influenza vaccine was delayed, and we did not attempt to evaluate the timing of vaccination with regard to the onset of influenza. Nonetheless, we wholeheartedly agree that our data confirm the need for better influenza-vaccine formulations.

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1. Walsh EE, Cox C, Falsey AR. Clinical features of influenza A virus infection in older hospitalized persons. J Am Geriatr Soc 2002; 50:1498-503.
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Treatment of Mild Asthma

TO THE EDITOR: Boushey et al. (April 14 issue)[1] report that regularly scheduled treatment with budesonide for mild persistent asthma has no significant advantage over intermittent short-course treatment. We compared data from a large pediatric survey of prescriptions for antiasthma drugs,[2,3] involving seven Italian regions, with the same kind of information from our region, Friuli-Venezia Giulia. In our region, ours is the regional referral center for pediatric asthma, and we suggest that short courses of controller therapies are preferable to prolonged treatments.[4] In our region, the number of prescriptions for inhaled corticosteroids in one year (2003) for children up to 13 years of age was one third as high as in other Italian regions (0.47 vs. 1.46 packets per child, respectively), and the number of prescriptions for montelukast was less than half as high (0.11 vs. 0.26 packet per child, respectively). Nevertheless, the amount of reliever drugs (albuterol) dispensed to each child with asthma (i.e., the major indicator of asthma exacerbations) in our region was similar to that in the other regions (1.42 vs. 1.44 packets per child, respectively). These findings in 88,736 children with asthma seem to support the conclusions of Boushey et al. in a study of adult patients.

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TO THE EDITOR: Boushey et al. conclude that as-needed corticosteroids may be adequate to treat mild persistent asthma on the basis of a study in which daily budesonide, daily zafirlukast, or intermittent treatment failed to show a difference in morning peak expiratory flow (PEF), the primary efficacy variable, and in asthma exacerbation. A conclusion based on failure to show a difference in a study not designed as a noninferiority study has limitations.[1] The study did not have a concurrent control group that could validate the sensitivity of morning PEF. Such a control group would have been useful because prebronchodilator forced expiratory volume in one second (FEV_1), which is another surrogate for asthma control, and some results with respect to patient-reported outcomes and markers of disease activity were significantly superior with daily budesonide as compared with other treatments. In this study, the pretreatment PEF and FEV_1 results were not similar — in contrast to many clinical studies with corticosteroids in which results for these two related measures of lung function were similar.[2] It is possible that daily budesonide was better than the other treatments, but morning PEF was not sufficiently sensitive to show the difference.

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1. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ 1995;311:485.
2. Physicians' desk reference. Montvale, N.J.: Thomson PDR, 2005: 629, 1494, 1722.

TO THE EDITOR: We welcome Boushey and colleagues' contribution to evidence on the management of mild persistent asthma, which occurs in a large patient population in Westernized countries. However, we urge caution in interpreting these data. The study intervention was not simply intermittent inhaled corticosteroids; it also included regular medical review, written action plans, immediate availability of medication for exacerbations, and prior assessment of suitability for this approach. Furthermore, given that the aim of the study was to examine the effects of 12 months of treatment on asthma control, the change in the morning PEF between two short periods was not the ideal primary outcome variable, and the importance of improvement in the number of symptom-free days appears to have been undervalued. Final-

ly, without regular monitoring, it would be unwise to assume that exacerbations were not underreported, when they were diagnosed only on the basis of the patient's implementation of a complex, high-dose, symptom-based action plan and acknowledged untreated symptomatic episodes. Further studies are needed to identify the circumstances in which intermittent inhaled corticosteroids can achieve optimal outcomes in mild asthma.

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Dr. Jenkins reports having received honoraria for educational presentations, funding for clinical research, travel expenses, and payment for service on advisory boards from AstraZeneca and GlaxoSmithKline. Dr. Marks reports having received honoraria for educational presentations from AstraZeneca and GlaxoSmithKline and research funding from GlaxoSmithKline. Dr. Reddel reports having received funding for clinical research from AstraZeneca and funding to attend conferences from AstraZeneca and GlaxoSmithKline. The Woolcock Institute of Medical Research receives educational grants and research funding from AstraZeneca and GlaxoSmithKline.

TO THE EDITOR: The study by Boushey and colleagues serves to highlight further the disconnection between airway caliber and airway inflammation. Although no apparent change in airway caliber was demonstrated in the three treatment groups, patients who did not have the benefit of regular inhaled corticosteroids had significantly higher levels of exhaled nitric oxide, more eosinophils in sputum, and greater bronchial reactivity, indicating underlying ongoing untreated airway inflammation. No one is certain of the long-term consequences of leaving persistent airway inflammation unchecked, especially when inflammation itself forms the very basis of asthma and contributes to airway remodeling. This study should therefore act as a catalyst for further research, rather than as a source of definitive support for pro re nata use of corticosteroids in mild asthma with persistent airway inflammation.

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TO THE EDITOR: When comparing the efficacy of different treatment strategies in asthma, it is important to choose the appropriate end points that are more likely to influence decision making in clinical practice. Boushey et al. chose morning PEF as the primary end point in a comparison of the efficacy of regular and intermittent inhaled corticosteroid therapy. We do not believe that morning PEF is the most important measure that influences decision making. Lung function does not always correlate well with clinical outcomes.[1] Johansson et al.[2] recently reported that patients with asthma ranked symptom-free days as the most important attribute of asthma treatment. Boushey et al. report that regular inhaled steroids increased symptom-free days by almost a month, as compared with intermittent therapy. In addition, they report significant improvements in airway hyperresponsiveness and reduction in underlying airway inflammation. Had these variables — which we believe are more relevant in decision making in clinical practice — been chosen as primary end points, Boushey et al. would have concluded that regular treatment with inhaled corticosteroids is better than intermittent treatment.

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Drs. Raghupathy, Brashier, and Salvi report involvement in clinical trials for Cipla (India).

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THE AUTHORS REPLY: We appreciate the comments of Dr. Berti and colleagues. If confirmed, their findings would suggest that intermittent therapy may be an acceptable strategy for a subgroup of children with asthma. Dr. Chowdhury is correct that our study was not designed as a noninferiority trial. However, we found that even at the limits of the confidence intervals, the between-group differences in exacerbation rates may not have been great enough to justify advocating regular therapy in the population studied. Although morning PEF was selected as the primary outcome variable, other indexes of asthma control were included a priori in our analysis plan. The change in post-broncho-

dilator FEV_1 was selected as a possible indicator of permanent or, at least, poorly reversible change in airway caliber.

Several correspondents refer to the potential value of an increase in symptom-free days. In the absence of important differences in exacerbation rates or in the change in post-bronchodilator FEV_1, this increase means simply that patients may be allowed to decide whether the gain in symptom-free days justifies taking daily therapy. This decision will no doubt be influenced by the patient's perception of the importance of fewer days of symptoms as compared with the inconvenience, cost, and perceived toxicity of treatment.

Dr. Jenkins and colleagues urge that care be taken in generalizing our findings to settings in which patients are not seen regularly, instructed in an action plan, or provided with medication to use when their asthma symptoms flare. We agree. We do not agree that exacerbations were underreported, since inquiry was made about such events every six weeks. We do agree, however, that further studies to examine the applicability of our findings would be useful.

Dr. Raghupathy and colleagues claim that reduction in markers of airway inflammation is a more relevant end point for guiding clinical decision making. As we reported, markers of inflammation are increased in patients with sustained spontaneous clinical remission of asthma.[1,2] We would question the relevance to clinical practice of aiming treatment at normalizing a laboratory test if that normalization were not associated with improvements in the quality of life in the present or a reduction of risk in the future. We thus agree with Dr. Lee that additional research is needed on the long-term consequences of checking the very mild inflammation found in patients such as those enrolled in our study.

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Since publication of his April 14 article, Dr. Boushey reports having received consulting fees from Altana.

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THE EDITORIALIST REPLIES: The provocative article by Boushey et al. challenges the "politically correct" doctrine of current guidelines recommending continuous treatment of mild persistent asthma with inhaled steroids. Thus, it is no surprise that it has generated discussion. Three letters addressed to Boushey et al. have also been sent to me for comment, as they touch on issues discussed in my accompanying editorial.[1] Jenkins et al. suggest that the selection of patients and the management plan may have contributed to a masking of differences among treatments. I agree that the careful selection of persons with mild persistent asthma — so mild that it did not require regular treatment after almost 20 years — and the management plan offered to all subjects may have contributed to an inability to detect differences among treatments for many of the outcomes examined.

Jenkins et al., Raghupathy et al., and Lee criticize the selection of morning PEF as the primary outcome, suggesting that the use of patient-centered outcomes (e.g., symptom-free days) would have led to different conclusions and a different clinical message. Although I, too, would have preferred a patient-centered outcome as the primary outcome, I believe that the clinical message of this report would not have changed. The only difference would have been the order of description of the results: more days of symptoms but no difference in PEF and other relevant secondary outcomes.

Dr. Lee is concerned that leaving persistent inflammation uncontrolled with intermittent treatment, rather than regular treatment, may be associated with adverse long-term events, particularly airway remodeling. As I stated in my editorial, there is no evidence that mild chronic asthmatic inflammation is responsible for the progression of the disease. We still do not know whether chronic persistent inflammation, which is present not only in persons with mild asthma but also in those with nonasthmatic rhinitis,[2] including very young children,[3] represents an offensive abnormality that needs to be suppressed even in asymptomatic persons.

One point we all agree on is that we need a properly designed and powered study that is comprehensive enough to answer the fundamental questions raised by Boushey et al. Until we have the

results of such a study, any clinical recommendation is necessarily based on limited evidence.

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Hyponatremia in Marathon Runners

TO THE EDITOR: Almond et al. (April 14 issue)[1] excluded an important variable in their assessment of hyponatremia in marathon runners. Excess fluid intake is clearly a contributor to low serum sodium concentrations,[2] but numerous long-distance runners in the study population ingested high-sodium endurance gels. These popular supplements were offered by the race sponsors at mile 17 of the Boston Marathon or carried by the runners and ingested ad lib. Most of the gels contain 40 to 100 mg of sodium per packet of 32 to 41 g. The typical marathoner who completes the race in four to five hours might ingest a packet every hour, roughly equivalent to 160 to 500 mg of sodium per race. In contrast to hypotonic sports drinks and water, fluids with high sodium concentrations can counter hyponatremia if used appropriately,[3] an effect not investigated in this study.

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TO THE EDITOR: Almond et al. demonstrate that hyponatremia, a sodium concentration of less than 135 meq per liter, is a common complication in marathon runners. Symptomatic hyponatremia can be fatal if not treated with hypertonic saline. Despite the proven safety of hypertonic saline for the treatment of hyponatremic encephalopathy,[1-3] its use has been marginalized in the literature,[4] resulting in confusion with regard to therapy. We described noncardiogenic pulmonary edema due to increased intracranial pressure from cerebral edema as a presenting feature of hyponatremic encephalopathy in marathon runners.[5] Six patients treated with hypertonic saline survived without neurologic sequelae, whereas one patient who was not treated died. We therefore recommend that any runner who exhibits signs of respiratory insufficiency, confusion, obtundation, nausea, and vomiting should be evaluated for hyponatremia, with a rapid method on site in a medical tent. We suggest that runners with hyponatremia be treated with 100 ml of 3 percent sodium chloride solution for 10 minutes to raise the serum sodium concentration rapidly by 2 to 3 meq per liter and to decrease brain edema. This therapy should stabilize the patient's condition before transfer to the hospital and neuroimaging studies but should not result in complications.

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TO THE EDITOR: Almond and colleagues correctly warn that weight gain during marathons may cause acute hyponatremia. Nevertheless, the degree of water retention may be underestimated if assessed on the basis of weight gain because of

the oxidation of about 0.5 kg of the fuel, glycogen plus triglyceride. Since each kilogram of glycogen associates with about 3 kg of "bound" water, this release of water can cause hyponatremia without weight gain if the water is electrolyte-free.

There are three problems associated with the interpretation of postrace plasma sodium concentrations. First, water retained in the gastrointestinal tract contributes initially to weight gain, but later, when absorbed, the water contributes to hyponatremia if there is vasopressin activity.[1] Second, when water absorption is rapid, the venous plasma sodium concentration is appreciably higher than in the arterial sodium plasma concentration (a measure of the sodium concentration to which the brain is exposed) in a simultaneously drawn sample.[2] Third, if the effective osmolality in myocytes rises appreciably when L-lactic acid accumulates during a final sprint, there can be a sudden but transient rise, by about 10 mM, in the venous plasma sodium concentration.[3] Therefore, physicians should recognize that the postrace venous plasma sodium concentration might appreciably underestimate the potential severity of hyponatremia in runners who have gained weight.

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THE AUTHORS REPLY: As Dr. Peate points out, it is possible that differences in sodium intake before, during, or after the race help to explain some of the observed variation in sodium levels among runners with similar degrees of weight gain. Although Twerenbold et al. found a difference,[1] other studies analyzing the effect of salt intake on plasma sodium levels during prolonged exercise have shown mixed results.[2-4] It is unclear whether the lack of a consistent benefit can be explained by methodologic issues or by the pathophysiology of hyponatremia, which may include a component of antidiuresis, a mechanism that may be less amenable to correction with sodium. Nevertheless, these reports document a low incidence of hyponatremia among runners who did not gain weight. Although the role of salt supplementation merits further study, the available evidence indicates that the most effective way to prevent hyponatremia during marathon running is to avoid a positive fluid balance.

We agree with Dr. Ayus and colleagues that hypertonic saline is the treatment of choice for symptomatic patients with severe hyponatremia, and that treatment with hypotonic fluids for presumed hypovolemia could be detrimental. Rapid point-of-care testing to establish the serum sodium level is invaluable in determining the appropriate fluid therapy for ill marathoners, especially because the clinical presentation of dehydration can be similar to that of hyponatremia.

Dr. Halperin and colleagues point out that weight gain may underestimate the degree of free water excess in runners, if one assumes that the postrace weight should be lower than the prerace weight on the basis of glycogen and fat metabolism, irrespective of fluid balance. We agree with Dr. Halperin and colleagues, whose suggestion may account for the small group of runners in our study who had hyponatremia but did not have an appreciable weight change. Indeed, the optimal fluid balance for marathoners may involve the loss of a small percentage of body weight during the race.

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Inflammation, Atherosclerosis, and Coronary Artery Disease

TO THE EDITOR: In his review of inflammation, atherosclerosis, and coronary artery disease, Hansson (April 21 issue)[1] focuses on T cells, macrophages, and mast cells as the cellular components of the immune system that play a key role in ischemic heart disease. However, he omits a possible role for neutrophils.

Several lines of evidence support the possibility that these cells are involved in this condition. Early studies showed a strong positive correlation between peripheral-blood neutrophil counts and the risk of acute myocardial infarction[2] and documented the presence of activated circulating neutrophils in acute coronary syndromes.[3] Furthermore, infiltration by neutrophils of culprit lesions in acute coronary syndromes has been shown.[4] Finally, the prognostic value of plasma levels of myeloperoxidase — an enzyme mainly secreted by neutrophils — to identify patients with chest pain who are at risk for cardiac events further reinforces the role of these cells in the pathogenesis that underlies coronary artery disease.[5]

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TO THE EDITOR: Hansson's review does not mention aspirin among the therapeutic options for coronary artery disease. Aspirin was found to reduce the risk of a first myocardial infarction by 44 percent.[1] Ridker et al.[2] found that the beneficial effect of aspirin was directly related to baseline levels of C-reactive protein, with the greatest value among men with the highest baseline concentrations of C-reactive protein. Although the antiplatelet effect of aspirin may be modified by an underlying inflammation, the study by Ridker et al. suggests the possibility that the beneficial effect of aspirin in the prevention of coronary artery disease may be attributed at least in part to its antiinflammatory property.[3]

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DR. HANSSON REPLIES: Atherosclerosis is indeed a complex disease. Several cell types are involved in its pathogenesis, and many drugs have been used to treat it or prevent its complications. In my review, I discussed the role of macrophages, T cells, mast cells, and endothelial and smooth-muscle cells in the formation and progression of atherosclerotic lesions. García de Tena suggests that neutrophils may also be important participants in the development of disease. This is an interesting suggestion and has received some support from the clinical and histopathological studies he cites. However, myeloperoxidase, the neutrophil enzyme he proposes as a prognostic marker, is produced not only by neutrophils but also by macrophages present in lesions.[1] On balance, the role of neutrophils remains unclear and should be the topic of further investigations.

Kriszbacher et al. point out that aspirin is a valuable therapeutic agent in coronary artery disease. This is certainly true; there is abundant work in the literature supporting the use of aspirin, which is used throughout the world to prevent coronary events. Many years ago, Vane discovered that aspirin inhibits prostaglandin synthesis.[2] It is now well established that the formation of thromboxane A_2, which has aggregatory effects on platelets and which is a vasoconstrictive prostaglandin, is inhibited when aspirin acetylates cyclooxygenase.[3] In addition, aspirin at a high concentration blocks signaling by nuclear factor-κB and thus inhibits inflammation.[4] Whether the low doses of aspirin used for preventing coronary events are sufficient to inhibit inflammation remains controversial.

Therefore, although I concur with Kriszbacher et al. that low-dose aspirin should be used in coronary artery disease, I am less convinced that its beneficial effect is due to its antiinflammatory properties. For this reason and because my task was to review mechanisms of disease rather than current therapy, aspirin was not discussed in my article.

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Physician as Serial Killer

TO THE EDITOR: I am extremely disturbed by the implications of Esmail's comments in his Perspective article on the case of Harold Shipman (May 5 issue)[1]: Esmail calls for a more questioning attitude toward doctors and better systems for monitoring their work. Dame Janet Smith, the judge who chaired the Shipman inquiry, has been even more outspoken about the need to increase regulation of the profession. But if one asks of which group of doctors Shipman was typical, the answer is none. Shipman was indeed a "one-off," a serial killer who happened to be a doctor. There is undoubtedly a case for better regulation of death certification and of the storage of controlled drugs, but we must resist this extraordinary notion that the Shipman case somehow justifies throwing even more ropes around our much-maligned profession. Many British family doctors are already running scared of the risk of "Shipman" allegations and are unwilling to leave sick, elderly people in the community, preferring to admit them to the hospital given the slightest excuse, simply for fear of criticism. This response cannot be in anyone's best interest.

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1. Esmail A. Physician as serial killer — the Shipman case. N Engl J Med 2005;352:1843-4.

TO THE EDITOR: The article by Esmail is especially chilling since there was nothing about Dr. Shipman's behavior that suggested a problem. This was not the case with Michael Swango, who killed more than 35 patients. He was suspected of wrongdoing at each stage of his career. When he was a student, the Department of Obstetrics and Gynecology at Southern Illinois University, to its credit, "checked the box" indicating that it had reservations about his fitness for medical practice. Others on the faculty believed that it was unfair to fail a student at the end of four years of medical school, and their support allowed Swango to graduate. Over the next 10 years, suspicion of his misdeeds was ignored by a series of supervisors. James Stewart's gripping account of this disaster, *Blind Eye*,[1] is a worthy read for those who evaluate medical trainees.

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Medical Mystery: Bradycardia — The Answer

TO THE EDITOR: The medical mystery in the June 2 issue[1] involved a 49-year-old man who reported fatigue, arthralgia, and headache, along with a two-day history of chest pain; an electrocardiogram (Fig. 1) had been obtained. The patient was hospitalized. Myocardial infarction was ruled out. The findings on echocardiography were unremarkable. A serologic analysis for Lyme disease was positive, with confirmation by Western blotting. On further questioning, the patient noted that he had received a tick bite six weeks earlier and that it had been associated with a brief febrile illness without a rash.

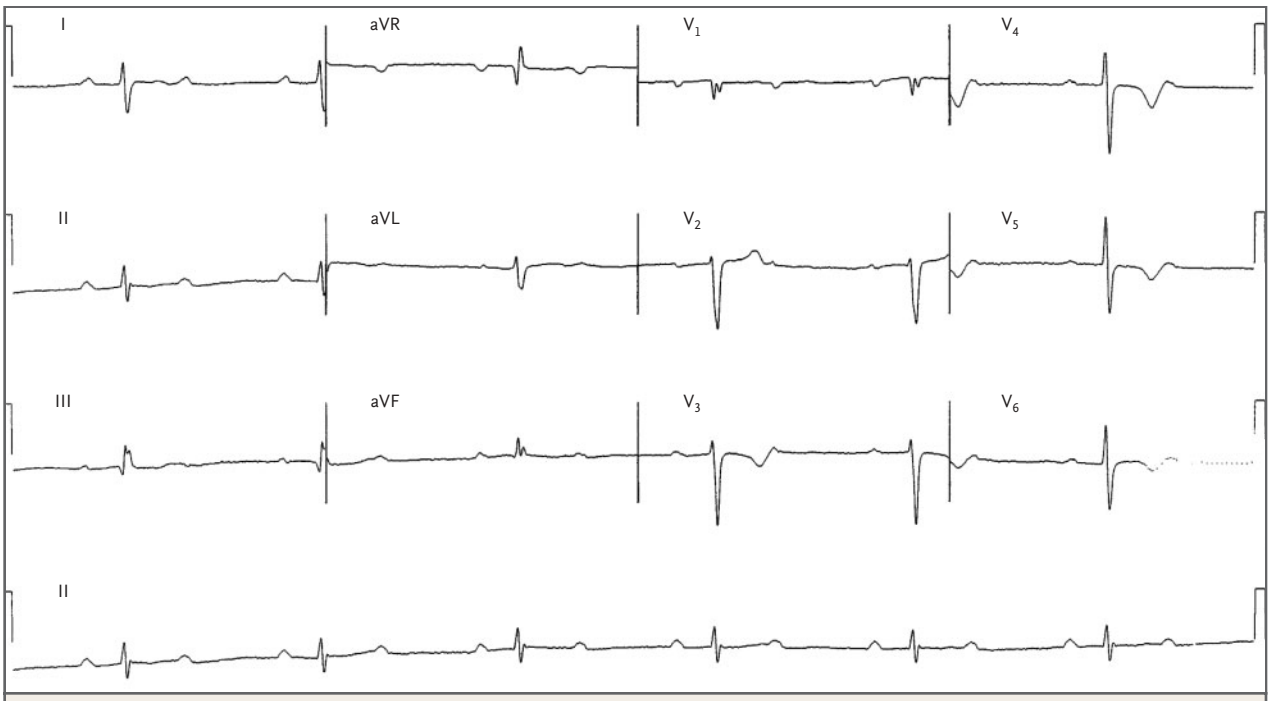

Figure 1. **Electrocardiogram from a Man with Fatigue, Arthralgia, Headache, and Chest Pain.**

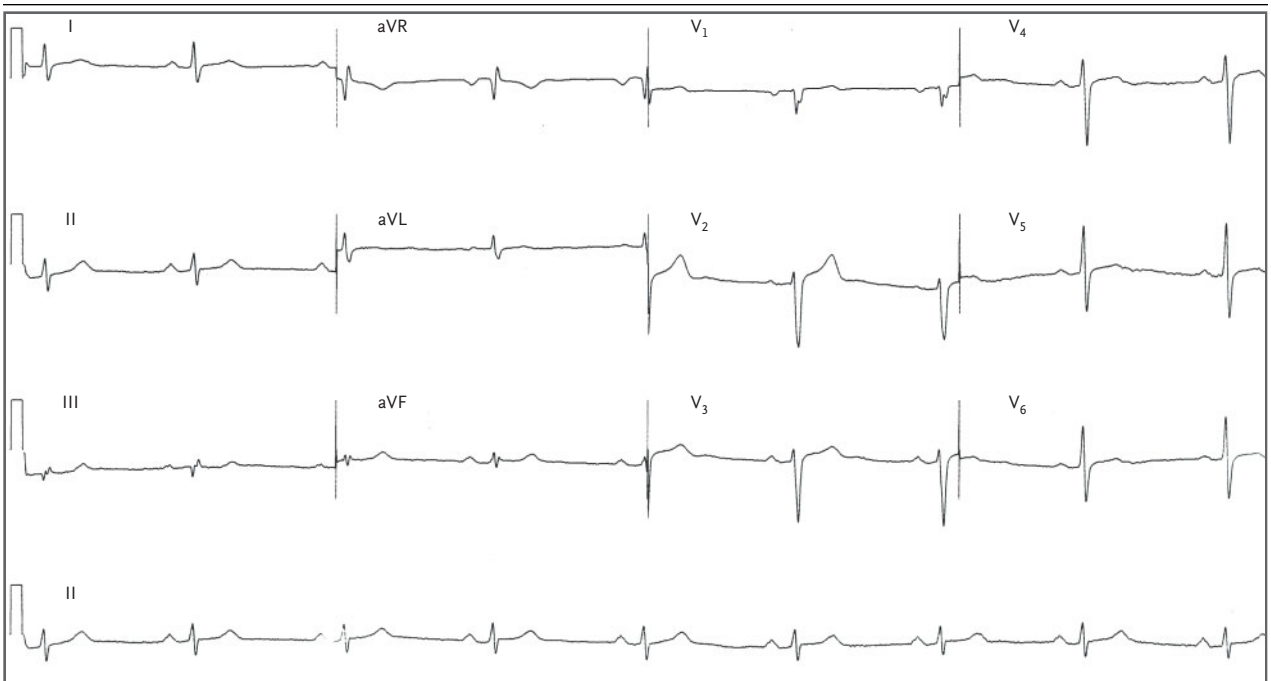

Figure 2. **Electrocardiogram after Treatment with Ceftriaxone for Lyme Disease.**

Intravenous administration of ceftriaxone (2 g daily) was begun. On day 4, the second-degree heart block resolved, but the first-degree heart block and ischemic changes persisted. A nuclear-isotope study with dipyridamole revealed an anterior lateral reversible defect, thought to be consistent with ischemia or myocarditis. The results of cardiac catheterization were normal. Two weeks after intravenous ceftriaxone therapy, the electrocardiogram was normal (Fig. 2) and the patient was well. Heart block associated with Lyme disease typically responds to antimicrobial therapy and rarely requires placement of a permanent pacemaker.

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Editor's note: We received 1575 responses to this medical mystery; 59 percent were from physicians in practice, 23 percent from physicians in training, 10 percent from medical students, and 8 percent from other readers. Forty-nine percent of the responses were from 79 countries outside the United States. Forty-three percent of the respondents correctly diagnosed Lyme disease, whereas 25 percent suggested a cardiac-conduction abnormality, and 16 percent suggested myocardial ischemia. Others provided explanations that included drug toxicity (e.g., due to atorvastatin), in 3 percent of the responses; endocrine dysfunction (e.g., hypothyroidism), in 3 percent; and other diagnoses (e.g., endocarditis, acute rheumatic fever, Chagas' disease, and sarcoidosis), in 10 percent. We received many insightful comments, including the following:

> The high degree of atrioventricular nodal block in combination with constitutional symptoms, arthralgia, and headache all point toward a diagnosis of Lyme disease. That he presented in June to a health care facility in Connecticut clinches the diagnosis!
>
> — Toby Maher, M.R.C.P.

> Oh the beautiful springtime in Connecticut!
> The flowers, the bees, the mice, the deer,
> and the tick.
> Don't rush to a pacemaker;
> IV ceftriaxone will do the trick.
>
> — Thomas J. Lester, M.D.

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Natalizumab and Progressive Multifocal Leukoencephalopathy

THE BRIEF REPORTS ON NATALIZUMAB WERE REFERRED TO BIOGEN IDEC, THE MANUFACTURER, WHICH OFFERS THE FOLLOWING RESPONSE: After learning of one confirmed and one suspected case of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab, Biogen Idec and Elan quickly notified the Food and Drug Administration (FDA) and other regulatory authorities. We worked closely with the FDA to understand the significance of these findings and to determine the appropriate action. On February 28, we voluntarily suspended all dosing and marketing of natalizumab; swift and decisive action was guided by our commitment to patient safety. Immediate efforts also included a comprehensive review of all adverse events to search for unrecognized occurrences of PML. We identified as suspicious a report of malignant astrocytoma and requested a reevaluation. The case was subsequently confirmed to be PML.[1]

The review of data on these patients, who are described in this issue of the *Journal*,[1-3] is part of a larger analysis under way in consultation with regulatory authorities and the National Institutes of Health to assess the risk of PML in natalizumab-treated patients. An independent panel with expertise in the diagnosis and management of PML is reviewing all suspicious and ambiguous findings to evaluate them for possible PML. A better understanding of the risk of PML will be possible only once the evaluation is complete. We hope to share findings from this evaluation by the end of the summer.

Unfortunately, we know little about PML and JC virus, but important observations can be gleaned from these case reports. One report suggests that clinical PML may be preceded by JC viremia.[1] Another demonstrates that PML is not uniformly fatal.[2] It is possible that testing for the appearance of JC virus in plasma, along with a high degree of clinical sus-

picion, will permit early diagnosis and discontinuation of natalizumab therapy and allow patients to recover. Similar findings have been reported for BK virus, a related polyomavirus that infects transplant recipients.[4]

Multiple sclerosis is a serious and disabling neurologic disease with limited therapeutic options. Since the suspension of natalizumab, we have heard expressions of frustration and disappointment from patients and others in the multiple sclerosis community. We understand that for many, natalizumab provided new hope for the management of this difficult disease; given these events and the efficacy and otherwise good safety profile of natalizumab, the importance of better defining potential risks of its use will be key to understanding its place in therapeutics.

We thank patients, physicians, and the entire multiple sclerosis community for their continued patience and support during the past few months. We remain firmly committed to a thorough evaluation of the safety profile of natalizumab so that we may provide physicians and patients with the necessary information to make informed benefit–risk decisions about their multiple sclerosis therapy.

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This letter was published on June 9, 2005, at www.nejm.org.

BOOK REVIEWS

MY MOTHER'S HIP: LESSONS FROM THE WORLD OF ELDERCARE

By Luisa Margolies. 339 pp. Philadelphia, Temple University Press, 2004. $66.50 (cloth); $22.95 (paper). ISBN 1-59213-237-5 (cloth); 1-59213-238-3 (paper).

American medicine increasingly reflects the face of elder care. The proportion of the population over the age of 65 increased throughout the 20th century, and it will increase markedly over the next two decades. Geriatric patients are the largest group of health care consumers, and they use an ever increasing portion of the care provided in emergency rooms, operating rooms, intensive care units, and rehabilitation centers. *My Mother's Hip*, by Luisa Margolies, provides a description of elder care akin to Hans Christian Andersen's fairy tale "The Emperor's New Clothes," with great monetary expenditure doing little to cloak our patients' naked suffering.

Margolies is a medical anthropologist, and she applies the techniques of that discipline to an examination of the final months of her mother's life. The book consists of eight chapters, seven of which are followed by a "lesson." In the chapters, the author uses ethnographic methods to examine her mother's progress through the health care system after she has bilateral hip fractures. The lessons provide didactic information about the major events in the preceding chapters, covering topics such as hip fracture, delivery of care, and advanced directives. The lessons will be of greatest interest to lay readers and health care providers without specialized knowledge. The chapters, rather than the lessons, were the parts that I found most interesting.

Margolies's tale illustrates both the phenomenal success of medicine in the treatment of disease and its profound failure in the treatment of individual persons. Her mother's many medical problems — polymyositis, rheumatoid arthritis, osteoporosis, bilateral hip fractures, pulmonary fibrosis, and pneumonia — were treated with state-of-the-art medical care, resulting in immediate physical benefit. Yet Margolies views the medical system as having failed her mother. At first glance, one might attribute this belief to a daughter's grief over her mother's inevitable death. Or one might assume that the author is chronically dissatisfied, given her litany of complaints about multiple providers at multiple facilities. However, to make these assumptions would be to overlook the dilemma the author is trying to share with us — the extent to which patients, families, and the health care system are stressed, and the degree to which the system fails, under the weight of chronic disease that results from our very successes.

Rehabilitation and end-of-life care are at the crux of this dilemma. Both issues involve the interface of disease with the social and environmental contexts; one has the goal of optimizing functional outcomes and the other the goal of ensuring death with dignity. Rehabilitation arose from the need to treat traumatic injury; thus, standard rehabilitation methods poorly fit the progressive disability, from multiple causes, that is typical of advanced age. Palliative care is dependent on acceptance of the imminence of death and on cultural attitudes about death; thus, the hospice model poorly fits those for whom death is uncertain, who are having difficulty accepting death, or whose cultural attitudes are profoundly different from the norm. This book underscores the importance of the need for further research on topics such as the strain on caregivers, the functional trajectory of illness and recovery in elderly patients, and the interface of religion and disease.

Although Margolies raises important issues, I found her insight into the solutions somewhat limited. She has an idealistic view of the state of elder care before Medicare became available. Forty years ago, her mother would not have survived bilateral hip fractures to have the post-acute care that Margolies finds problematic. The sentiments she ascribes to people with physical disability are simplistic; for example, she states, "Nothing is more painful than the day the chronically ill person realizes he or she cannot manage alone." Factors such as culture and personal history influence the myriad ways in which people adapt to chronic illness. For example, help from others may not be viewed negatively if it assuages loneliness or reinforces important family ties. Margolies does not address the philosophical question of where the responsibility

of medicine to relieve suffering ends and that of society and of the individual person begins. Nonetheless, this very readable book offers a unique view of the effect that illness has on the entire fabric of a patient's life. It will be of interest to both physicians and nonphysicians involved in elder care, as well as to the elders themselves.

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INCIDENTAL FINDINGS: LESSONS FROM MY PATIENTS IN THE ART OF MEDICINE

By Danielle Ofri. 181 pp. Boston, Beacon Press, 2005. $23.95.
ISBN 0-8070-7266-4.

In her first book, *Singular Intimacies: Becoming a Doctor at Bellevue* (Boston: Beacon Press, 2003), Danielle Ofri describes how it was to be a medical student at Bellevue Hospital in New York. Now, in *Incidental Findings*, Ofri tells how it is to be an attending physician on one of the general medical services of Bellevue, a large (1200-bed) city hospital with more than 25,000 admissions and 400,000 clinic visits each year.

After finishing her residency at Bellevue, Ofri takes time off to travel and supports herself as a locum tenens whenever she needs money. In a clinic on the Gulf Coast of Florida, she is not permitted to treat hypertension in a Honduran fruit picker because he doesn't have medical insurance. She is told by the medical director of a facility in an unnamed New England town, "We are a Catholic medical center. . . . Do you have any issues with that?" Ofri, puzzled, wonders whether he asked her this because she looked Jewish. In a village in New Mexico, she wants to treat disfiguring acne with isotretinoin in a Navajo woman who has had a tubal ligation, but the medication is not available. ("Where did I get the absurd notion that I might be a healer?")

Back in Manhattan after her *Wanderjahr,* Ofri picks up the thread of her career as an attending physician in internal medicine. She has "the odd sensation of making medical decisions without the requirement, or even the convention, of discussing them with someone else." In the outpatient clinic, her first assignment, a new patient arrives every 20 minutes: a Brazilian woman with crippling rheumatoid arthritis, a Dominican woman with a sore throat, a Bangladeshi man with diabetes, a Mauritanian woman with endless complaints, an Egyptian woman with diabetes, a Puerto Rican man with hypertension, an Ecuadorian woman with aches and pains everywhere, a Chinese man who turns out to have a metastatic brain tumor, a Puerto Rican man with emphysema, a man with schizophrenia, a man with arthritis, a woman with heartburn, a woman with hypertension — all this, plus the pettifoggery of a clerk who exploits a technicality to refuse to deliver a laboratory requisition. Welcome to New York City, Dr. Ofri.

There are memorable characters. Mr. McCreary, sent from the prison on Riker's Island with heart failure and severe diabetic neuropathy, is now well enough to return there. Huddled under the sheets with his neuropathic pain, he says, "You can't send me out feeling like this." An intern comments later to Ofri, "Those hyper-pain guys drive you crazy; nothing ever makes them feel better." There is also Mr. Karlin — articulate, urbane, 75 years old, and outraged by every indignity a big city hospital can offer. He is admitted after a fainting spell, but his main problem is severe leg pain. None of the resident physicians believe his story that an international expert on nerves has been treating him with monthly protein injections until the neurology consultant diagnoses an autoimmune neuropathy and points out that the "protein" is intravenous gamma globulin. Vindicated, Karlin tells Ofri that the neurologist was "the first guy around here that I've seen wearing a tie — a bow tie, no less," and "I used to give lectures on professionalism, and I think your motley crew could use a lesson or two." Then there is 29-year-old Cheryl Holloway, in the cardiac care unit with chest pain, a drug seeker who complains about a nurse whose name might well be Ratched — "That bitch won't give me my medicine" — and causes Ofri to fantasize escape into the music of a remembered concert at Carnegie Hall.

The 14 stories in *Incidental Findings* make clear Ofri's commitment — her moral duty — to her patients. The strands woven into them are humility, compassion, and respect for patients. Ofri reminds us that medicine is really about the bond between a patient and a physician. She writes in the final pages of her powerful book,

> Many industries have been automated, and medicine is no exception. I can't deny the increased efficiency provided by computerized

lab results, telemetry monitoring, and wireless e-mail. But no matter how much our field is pushed to streamline and to maximize efficiency, there is an asymptotic limit. In the end, medicine will always be about one patient and one physician together in one room, connecting through the most basic of communication systems: touch. In an age of breathless innovation, this is almost antediluvian. But medicine simply cannot be automated beyond this point.

Incidental Findings is a beautiful book. Ofri has enough faith in her patients, her profession, and herself to tell it all.

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INSIDE DEAF CULTURE

By Carol Padden and Tom Humphries. 208 pp. Cambridge, Mass., Harvard University Press, 2005. $22.95. ISBN 0-674-01506-1.

Young Women Learning Sign Language at a School for the Deaf, 1930s.

Mary Evans Picture Library.

THIS WELL-ORGANIZED AND CLEARLY written book provides a fascinating inside look at the development of Deaf culture. As noted in the introduction to the book, the authors use the convention of capitalizing Deaf when referring to members of a distinct culture — people who share features of a community within a community, most notably their fluency in sign language. When the word "deaf" is used more broadly to denote the condition of hearing loss, it is lowercased. This history of the development of the language and mores of Deaf people provides a basis for understanding the current climate in the Deaf world. Padden and Humphries expose the conflicts and discrimination the Deaf have faced over the years and the approaches they have used to surmount obstacles and survive as a community. The authors provide the historical background not only for its intrinsic value and interest, but also as a means to explore avenues that could ensure the future of the Deaf as they confront perceived threats to their culture, language, and way of life.

It is in addressing these threats that the authors — either unwittingly or with forethought — malign parents of children who are deaf and physicians and scientists in the hearing world who advocate cochlear implantation. The danger of extinction may indeed be real to those who live strictly within the Deaf community; however, the solutions to preserving that culture may also reside within the community, particularly in how the Deaf respond to the challenge of others with hearing loss who choose to live in the hearing world. The professionals in the field of cochlear implantation are not making choices; they are providing options for an alternative way of life.

It is no easy task to convince the majority populace that deafness is a culture, considering the fact that hearing is one of the five senses. The message of "different but equal and together" is critical to the goals set forth in this book, but allowing people to choose a lifestyle is equally compelling. Padden and Humphries's presentation of these marvelous insights into the history and development of the language and beliefs of the Deaf should be viewed as a welcome step in the quest to inform the hearing world of the rich and fertile culture of the authors' beloved community. The facts are powerful and can stand alone as a reminder of the Deaf community's right to exist and be recognized; they should not be weakened by the indictment of members of the hearing world.

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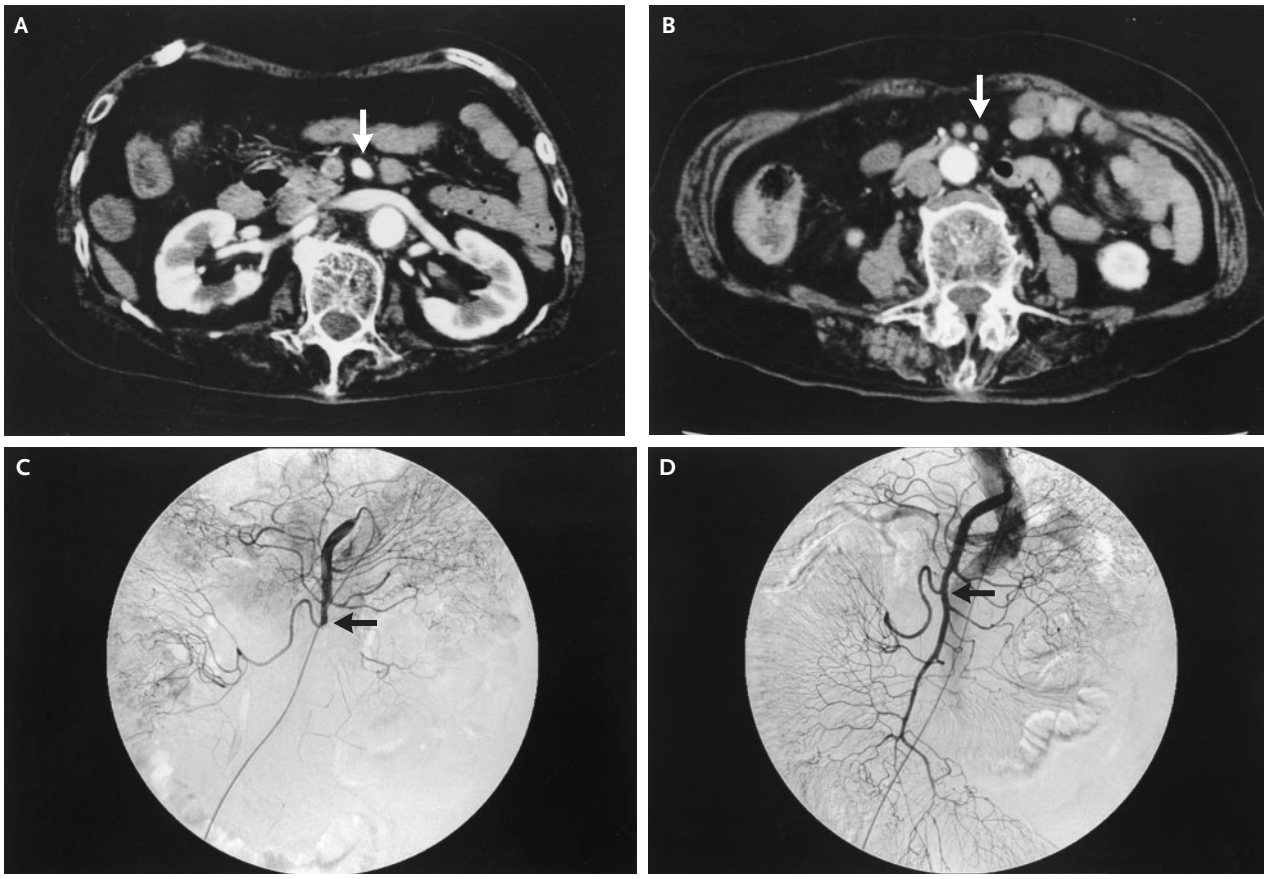
IMAGES IN CLINICAL MEDICINE

Transcatheter Treatment of Thromboembolism in the Superior Mesenteric Artery



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An 88-year-old woman with a history of hypertension and atrial fibrillation presented with an acute onset of severe abdominal pain, vomiting, and diarrhea. She had been taking warfarin for the atrial fibrillation for three years but discontinued the medication against the advice of her physician six months earlier because she was asymptomatic. The physical examination revealed diffuse abdominal tenderness without guarding or rebound. A computed tomographic scan of the abdominal area after the administration of intravenous contrast material showed occlusion of the superior mesenteric artery (Panels A and B, arrows). Abdominal angiography, performed within six hours of the onset of the patient's symptoms, showed complete occlusion of the superior mesenteric artery (Panel C, arrow). After an intraarterial injection of urokinase, transcatheter thrombus aspiration was performed, which resulted in the recanalization of the superior mesenteric artery and immediate relief of her abdominal pain. The intraarterial infusion of urokinase was continued for 12 hours. Follow-up angiography, performed one day later, showed complete recanalization of the superior mesenteric artery (Panel D, arrow). The postprocedural course was uneventful. After three months, the patient continues to do well taking warfarin therapy. Important factors that are associated with an increased risk of thromboembolic events in patients with chronic atrial fibrillation include congestive heart failure, hypertension, an age of 75 years or older, diabetes, and prior embolic events.