THE NEW ENGLAND JOURNAL OF MEDICINE

Volume 356 — April 19, 2007 — Number 16  (pp. 1601-1692 )

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Into the Woods
The FDA and the Case of Ketek
David B. Ross, M.D., Ph.D.

Three years ago, the Food and Drug Administration (FDA) approved the drug Ketek (telithromycin), lauding it as the first of a new class of antimicrobial agents that circumvent antibiotic resistance. Since then, Ketek has been linked to dozens of cases of severe liver injury, been the subject of a series of increasingly urgent safety warnings, and sparked two Congressional investigations of the FDA’s acceptance of fraudulent safety data and inappropriate trial methods when it reviewed the drug for approval. As a former FDA physician who was involved in the Ketek review, I believe there are lessons to be learned from an examination of the events surrounding the approval of this product.

Ketek is a ketolide antibiotic manufactured by Sanofi-Aventis and proposed for use in community-acquired respiratory tract infections. It was reviewed by the FDA three times (see timeline). During the first round, reviewers identified substantial safety concerns, including multiple potential drug interactions, unique effects on visual acuity, and an apparent association with hepatocellular hepatitis, with pathological characteristics resembling those caused by drugs that have been withdrawn from the market because of hepatotoxicity. A federal advisory committee asked Sanofi-Aventis to obtain additional safety data by conducting a study involving patients who were likely to receive Ketek if the drug were approved.

In the second review, the FDA examined the results of such a study. Known as study 3014, it was an unblinded, randomized, controlled trial comparing the incidence rates of hepatic, cardiac, and visual adverse events in patients receiving Ketek and those receiving amoxicillin–clavulanate. Sanofi-Aventis recruited more than 1800 physicians to conduct the study, many of them new to clinical investigation, and paid them as much as $400 per patient enrolled, primarily to cover the costs of recruiting and gathering research data; more than 24,000 subjects were enrolled. The study was completed in 5 months and purported to show that Ketek was as safe as the other treatment.

A routine FDA inspection of the practices of the physician who enrolled the most patients — more than 400 — uncovered fraud, including complete fabrication of patient enrollment. The inspector notified FDA criminal investiga-
tors, and the physician is currently serving a 57-month sentence in federal prison for her actions. Inspections of nine other sites enrolling high numbers of patients revealed serious violations of trial conduct, raising substantial concerns about the overall integrity of the study. In the end, 4 of the 10 inspected sites were referred for criminal investigation.

Despite these discoveries, FDA managers presented study 3014 to the advisory committee in January 2003 without mentioning the issues of data integrity. The managers have stated that they were legally barred from disclosing the problems to the committee because there was an open criminal investigation, but they have not explained why the data were presented at all, in view of the evidence of the study's lack of integrity. Unaware of the integrity problems, the committee voted 11 to 1 to recommend approval of Ketek.

The undisclosed problems with study 3014 led to a third review, during which FDA managers proposed using foreign postmarketing reports on Ketek as evidence of the product's safety, despite the unreliability of such data. Although drug sponsors are required to submit such reports as part of an application, it is extremely unusual to use these data to address critical preapproval safety issues in place of a controlled study. The postmarketing data submitted by Sanofi-Aventis were reviewed by the FDA without any verification of their accuracy or completeness, even though 3 months before the third review, FDA criminal investigators recommended examining whether Sanofi-Aventis had been involved in systematic fraud in connection with Ketek. The FDA never conducted the recommended investigation or reviewed study 3014–related records showing that Sanofi-Aventis was aware of potential fraud in the study when it submitted the results to the FDA.

The failure to look into or respond to concerns about integrity represented a marked deviation from FDA policies. Against this backdrop of concerns about both safety and fraud, critical questions also arose about the efficacy of Ketek, which had been examined only in noninferiority trials. Such trials are not designed to demonstrate directly a new intervention's superiority to an active control or a placebo but instead involve the selection of a maximum margin by which the new intervention may be less effective than older interventions but still be considered better than placebo. Throughout the 1990s, noninferiority trials had been standard procedure in the development of antimicrobial agents for the outpatient treatment of self-resolving respiratory tract infections. But by 2004, FDA workshops and advisory committee meetings on this topic had concluded that the use of noninferiority trials in this setting was not justifiable, since there is no evidence of a substantial treatment effect of antimicrobial drugs in self-resolving respiratory tract infections such as acute bacterial sinusitis and acute exacerbation of chronic bronchitis — the diseases for which clinicians most frequently prescribe antimicrobials, for which the market is largest, and for which treatment with Ketek was proposed.

Nevertheless, the FDA approved Ketek entirely on the basis of noninferiority trials. The reason given for the agency's continued acceptance of such trials in the study of

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### Ketek Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2000</td>
<td>Ketek New Drug Application submitted to FDA</td>
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<td></td>
<td>First advisory committee meeting</td>
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<tr>
<td>2001</td>
<td>Study 3014 started</td>
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<tr>
<td></td>
<td>Sanofi-Aventis learns of fraud in study 3014</td>
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<tr>
<td></td>
<td>FDA discovers fraud in study 3014</td>
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<tr>
<td>2002</td>
<td>Investigation of Sanofi-Aventis recommended by FDA agents</td>
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<tr>
<td></td>
<td>FDA investigators declare study 3014 unreliable</td>
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<tr>
<td>2003</td>
<td>First Ketek-associated case of acute liver failure found submitted to FDA</td>
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<tr>
<td></td>
<td>FDA restricts Ketek use 1 day before Congressional hearing</td>
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<tr>
<td>2004</td>
<td>Ketek approved</td>
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<tr>
<td>2005</td>
<td>FDA relabels Ketek</td>
</tr>
<tr>
<td>2006</td>
<td>3 Ketek-associated cases of acute liver failure made public; FDA publicly cites study 3014 as evidence of Ketek safety</td>
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<tr>
<td>2007</td>
<td>9 more Ketek-associated cases of acute liver failure found</td>
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**Figure 1**

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**April 19, 2007**
antibiotics for self-resolving respiratory tract infections was the need to stand by prior agreements with industry sponsors regarding adequate trial designs — the Ketek trials, after all, had been designed and largely conducted before the adequacy of noninferiority trials had been called into question. Once it had been established that such trials could not demonstrate efficacy, however, it might reasonably have been argued that the welfare of prospective patients ought to outweigh any promise to manufacturers. Yet the FDA accepted the trials without discussion of either the patients who might be exposed to a drug that had serious toxic effects — and for which there was no evidence of effectiveness — or the failure of the trials to meet the FDA’s own standards at the time of approval.

The review of Ketek was thus marked by pronounced departures from accepted review practices. In addition to the use of fraudulent data, the substitution of uncontrolled postmarket safety reports for controlled clinical trial data, and the acceptance of trials that could not show efficacy, there was also overt internal pressure brought to bear on FDA reviewers to alter their conclusions.

When the FDA approved Ketek on April 1, 2004, the approving officials stated in a memorandum that it was “difficult” to rely on study 3014 for approval but revealed neither the fact that they had known for more than a year about serious problems that compromised the study nor the conclusion by FDA investigators that fraud and a failure of monitoring by Sanofi-Aventis made the study unusable. In this memo, the foreign postmarketing data were put forward as an acceptable substitute for an adequate and well-controlled trial, without any discussion of the lack of precedent for this approach or the unreliability of such data. Nor did the officials discuss the problems involved with relying on noninferiority trials for treatments of self-resolving infections, the conclusions of previous FDA meetings on this issue, or the applicable FDA standards that had been violated.

Sanofi-Aventis declared in advertisements that Ketek had the most successful launch of any antibiotic in history. In February 2005, 7 months after the drug was introduced to the U.S. market, the first death from Ketek-associated liver failure — in a patient treated for a mild respiratory tract infection — was reported to the FDA. The only formal response was an internal safety review written months later that devoted a few paragraphs to the event.

In January 2006, FDA management learned of the impending electronic report of a cluster of three cases of Ketek-associated acute liver failure at a single medical center, one of them the fatal case that had been reported almost a year earlier. An emergency meeting of FDA senior managers resulted in a public announcement that the FDA regarded Ketek as safe; this announcement cited study 3014 as part of the evidence the FDA had relied on in approving the drug. References to this fraudulent study soon started to creep into the biomedical literature.

In February 2006, I and other reviewers alerted FDA senior management to the irregularities in the Ketek case. FDA management took no substantive actions. In an internal e-mail, one senior manager, though aware of the fraud in study 3014, defended the agency’s citation of it, stating that the review division responsible for Ketek had used it. (Three days after a Congressional hearing on Ketek, in February 2007, the FDA finally removed any mention of study 3014 from its Web site.)

In the face of Congressional subpoenas and unfavorable publicity, reviewers at the FDA were warned at a June 2006 meeting by Andrew von Eschenbach, then the acting FDA commissioner, not to discuss Ketek outside the agency. By this time, 23 cases of acute severe liver injury and 12 cases of acute liver failure, 4 of them fatal, had been linked to Ketek. By the end of 2006, Ketek had been implicated in 53 cases of hepatotoxic effects. The FDA did not relabel Ketek to indicate its possible severe hepatotoxicity until 16 months after the first liver-failure cases became public. The withdrawal of approval for two indications, acute bacterial sinusitis and acute exacerbation of chronic bronchitis, for which Ketek’s efficacy had never been demonstrated, did not occur until February 12, 2007 — only a day before the Congressional hearing on Ketek.

To date, the agency has not addressed the actions taken by FDA senior managers in dealing with Ketek, but the hearings recently convened by Congress suggest that it is ready to do so, as part of its efforts to resolve broader problems at the agency. If the case of Ketek leads to important reforms, then the drug may have done some good after all.

An interview with Dr. Ross can be heard at www.nejm.org. A letter to the editor from
Soreth and colleagues at the FDA appears on page 1675.

Dr. Ross is a clinical assistant professor at George Washington University School of Medicine and Health Sciences, Washington, D.C.


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Approving the Vagus-Nerve Stimulator for Depression
Miriam Shuchman, M.D.

The vagus-nerve stimulator (VNS), a device that is implanted by a neurosurgeon and sends intermittent electrical pulses to the brain, has been marketed in the United States since 1997 as an adjunctive therapy for the control of epilepsy. Debate is ongoing, however, over the use of the device in patients with refractory depression. Though the key clinical questions (Does it work? Is it safe?) seem straightforward, answering them is proving rather complicated. The Food and Drug Administration (FDA) approved the use of the VNS for depression in 2005, but in February 2007, the Centers for Medicare and Medicaid Services issued its preliminary decision not to cover it, citing a lack of scientific evidence of its efficacy, and Blue Cross–Blue Shield had previously turned it down for similar reasons, though both insurers cover its use for epilepsy.

The VNS consists of a round, battery-powered generator about the size of a cardiac pacemaker that is implanted in the chest wall and attached to wires threaded along the vagus nerve in the carotid sheath (see diagram). After surgery, doctors program the generator to pulse the nerve for 30 seconds once every 5 minutes. The FDA approved the VNS for the treatment of epilepsy after two clinical trials, conducted with patients acting as their own controls, showed that it reduced the rate of seizures by about 25% among patients with refractory epilepsy when used as an adjunct to anticonvulsant drugs. There were frequent side effects, due to the effects of the VNS on the laryngeal nerve — including hoarseness, coughing, dyspnea, and rarely, vocal cord paralysis or infection. The VNS was assessed as safe and effective for patients for whom medication alone had failed, and major insurers accepted its high price — about $25,000 for the device and the surgery to implant it.

But the indication of clinical depression was added to its label on the basis of less compelling data. In an initial open-label study, 18 of 59 patients with depression had a response to 12 weeks of VNS therapy plus medication. The patients in the trial had been depressed for a median of 6.6 years, and they had received treatment with antidepressants at least twice, and in some cases, many times. The manufacturer of the VNS, Houston-based Cyberonics, and psychiatrists who were using the VNS in patients with depression called the condition “treatment-resistant depression” and referred to it as “TRD” — as if it were a well-established diagnosis, though it does not appear in the Diagnostic and Statistical Manual of Mental Disorders and the notion of a severe, unresponsive form of depression is not universally accepted in the psychiatric literature. Other psychiatrists believe, instead, that depression is an episodic illness for some persons and a chronic condition for others.

A few of the investigators involved in the open-label study, including A. John Rush of the University of Texas Southwestern Medical Center and Mark George of the Medical University of South Carolina, applied to the National Institute of Mental Health for funding for a randomized, controlled, double-blind trial of VNS in depression. Peer reviewers gave the proposal a relatively high rating for scientific merit, but the company withdrew its pledge to supply the devices, so the independent trial could not be pursued. Cyberonics opted to fund
the study themselves, Rush said, because “they were very interested in speed, so the quicker they could get [the study] done the better,” in their view. The company-sponsored trial comparing active VNS treatment with sham treatment entailed implanting the device but not turning it on. This trial was randomized and blinded, and it showed a response rate of 15% for the active-treatment group and 10% for the sham-treatment group at 10 weeks; the difference was nonsignificant.

When Cyberonics asked the FDA to approve the VNS for treatment-resistant depression in late 2003, the agency’s review team replied that the trial results didn’t justify approval and recommended that Cyberonics conduct a new controlled trial. But company officials said that it was impossible to conduct such a study. In its place, they offered positive findings from longer-term observational studies involving nonconcurrent control subjects. Although the FDA review team believed that Cyberonics’s data had serious deficiencies, in June 2004, an FDA advisory panel took another look at the observational data. Before the meeting, the FDA conducted a routine training session to familiarize the panel members with the rules of evidence for devices, which differ from those for drugs. For drugs, the FDA requires efficacy to have been demonstrated in two randomized, controlled trials, but for devices, the evidence may come from “trials without matched controls, well-documented case histories conducted by qualified experts, and [case reports permitting conclusions] by qualified experts that there is reasonable assurance of the safety and effectiveness of a device.”

Rush, who led the controlled trial of the VNS in depression, told the FDA advisory panel that patients with treatment-resistant depression, like patients with refractory lymphoma, were “really at the end of the line.” Rush and other experts made repeated references to the need for new options for patients in whom several trials of antidepressant therapy, psychotherapy, or electroconvulsive therapy had failed — people for whom the VNS was a last resort. Five patients also delivered moving testimonials.

Richard Malone, a professor of psychiatry at Drexel University College of Medicine who served on the panel, argued that the company needed to prove the efficacy of the VNS in a controlled trial, but Rush said that it would be unethical to do so, because eligible patients would be too depressed to be taken off their medications and given only a placebo. Allowing patients to continue to take their antidepressants for the duration of a long-term trial wouldn’t solve the problem, he said, because doctors wouldn’t be able to alter the patients’ treatment regimens if their condition worsened.

FDA scientists had concerns about the safety of the VNS, since...
many adverse events — including suicides, suicide attempts, and worsening depression — had been reported in VNS trials in the United States and Europe. An FDA neurosurgeon who addressed the panel, Michael Schlosser, said that the proportion of patients with suicide attempts or completed suicides was high enough to raise alarms about possible “precipitation of suicide by this device” and that there was concern about possible cardiac risks, in view of episodes of arrhythmia, hypertension, bradycardia, and asystole that occurred during the trial of VNS in depression, as well as several sudden deaths of patients using the device for either epilepsy or depression. The panel, however, viewed the device as safe, apparently because it was already being used in patients with epilepsy. They voted five to two to approve its use in patients who had tried standard treatments for depression at least four times without a response.

The FDA is not obliged to accept the recommendations of its expert panels, however, and in this case, the agency sent Cyberonics a letter in August 2004 stating that because of the safety concerns, it didn’t intend to approve the VNS for depression unless the company provided more data from randomized, controlled trials to show that the benefits outweighed the risks. Cyberonics’s chief executive officer at the time, Robert “Skip” Cummins, told investors that staff members of the company then “talked and met with everyone at FDA who would listen.” Cummins said that they also spoke to members of Congress, after which several legislators questioned the FDA about the VNS.

With the FDA demanding more data, interactions between the agency’s VNS team and Cyberonics were “terrible,” according to FDA staff members. Despite the company’s lobbying efforts and its submission of more data, the review team concluded in November 2004 that it would not approve the VNS except as an investigational device. But Daniel Schultz, director of the FDA’s Center for Devices and Radiological Health, overruled his team. In an interview, Schultz said he “agonized” over this decision, but he didn’t think that the controlled trial recommended by FDA staff members was feasible — for the reasons Rush had discussed. In the end, he opted to approve the device, albeit with a relatively stringent requirement for postmarketing studies.

Senator Charles Grassley of Iowa, the ranking Republican on the Senate Finance Committee and a well-known critic of the FDA, heard of the disagreements within the agency and ordered an investigation. Grassley has historically championed FDA whistle-blowers who have brought drug-safety issues to light. His staff interviewed FDA employees, reviewed their e-mails, and issued a report stating that “more than 20 FDA scientists, medical officers and management staff” members disagreed with Schultz’s decision to approve the VNS. The report also quoted FDA staff members who said that Cyberonics officials had become verbally abusive toward them during the VNS review process.

Meanwhile, Cyberonics was busy on other fronts, touting the VNS’s prospects. Cummins told investors that 4 million Americans with depression could benefit from the device, though Maurizio Fava, a psychiatrist at Massachusetts General Hospital and an expert on difficult-to-treat depression, estimates the size of the eligible patient population at about 200,000. Last June, the company came under investigation by the Securities and Exchange Commission and the U.S. Attorney’s office in Manhattan for securities fraud. By November 2006, the probes had forced Cummins and the company’s chief financial officer to resign and the company to acknowledge problems with stock options going back several years.

In the nearly 2 years since the VNS therapy was approved for depression, the company hasn’t pursued another controlled trial, despite requests from its medical advisors to do so. Schultz thinks that one of the postmarketing studies the FDA required as a condition of approval — a double-blind, randomized evaluation of various amounts of electrical current — could nearly substitute for a controlled trial, since one treatment group is receiving a very low level of stimulation, similar to a placebo. However, the company told the FDA in January that the limited reimbursement available poses a threat to enrollment in the trial. To address this problem, Cyberonics now donates the devices and pays for their implantation.

Clinicians cannot know for sure whether the VNS works for depression, but the best evidence available to date suggests that it doesn’t. The larger question is whether the FDA’s standards for approval of medical devices are appropriately rigorous for products intended to treat mental illness. In panelist Richard Malone’s
view, the requirements should include two blinded, controlled trials of any device for the treatment of psychiatric disorders. “Regardless of whether it’s a device or a drug, the same criteria should be used,” he said.

This question of how best to judge devices is not about to go away. Several other “neurostimulators” will soon cross the FDA’s threshold — for example, repetitive transcranial magnetic stimulation devices designed to be used in place of electroconvulsive therapy for depression are in clinical trials, with one such device already submitted to the FDA, and an implantable deep-brain stimulator in use for Parkinson’s disease is being tested for the treatment of depression and obsessive–compulsive disorder. And Cyberonics itself is also going to come back for more: the VNS is now being tested as a treatment for anxiety disorders, Alzheimer’s disease, bulimia, and migraine headaches.

Dr. Shuchman is a national correspondent for the Journal.


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Transfusion Strategies in Pediatric Intensive Care Units

Questions remain regarding the timing and quantity of red-cell transfusions in pediatric intensive care units. This study involving stable, critically ill children showed that a restricted strategy (transfusion threshold, 7 g of hemoglobin per deciliter) was as safe as a liberal strategy (transfusion threshold, 9.5 g per deciliter). Rates of multiple-organ dysfunction were similar in the two study groups.

See P. 1609; Editorial, P. 1667

Effect of Torcetrapib on Carotid Atherosclerosis in Familial Hypercholesterolemia

Since torcetrapib, an inhibitor of cholesteryl ester transfer protein, markedly increases levels of high-density lipoprotein cholesterol and lowers levels of low-density lipoprotein cholesterol, in principle it might have a beneficial effect on atherosclerosis. However, in this clinical trial, torcetrapib had no beneficial effect on carotid atherosclerosis, as assessed by ultrasonographic measurement of carotid intima–media thickness. The reasons for this finding are unclear, but the drug did increase blood pressure slightly.

See P. 1620

Omeprazole before Endoscopy in Patients with Gastrointestinal Bleeding

In this randomized study of patients with upper gastrointestinal bleeding, infusion of omeprazole, as compared with placebo, before endoscopy reduced the incidence of endoscopic treatment (19.1% vs. 28.4%, P = 0.007) and, among patients with peptic ulcers, resulted in fewer actively bleeding ulcers and more ulcers with clean bases. These findings suggest that infused omeprazole is beneficial for patients with upper gastrointestinal bleeding who are awaiting endoscopy.

See P. 1631; CME, P. 1695

Targeted Therapy for Inherited GPI Deficiency

Inherited glycosylphosphatidylinositol (GPI) deficiency, characterized by splanchnic vein thrombosis and epilepsy, is caused by a mutation in the promoter region of PIGM. The mutation results in hypoacetylation of the promoter and reduced transcription of the gene. Therapy with sodium butyrate, a histone deacetylase inhibitor, increased PIGM transcription and controlled status epilepticus in a young patient with the disease.

See P. 1641

Fecal Incontinence in Adults

A 53-year-old woman presents with a history of intermittent fecal incontinence. Physical activity often precipitates an episode, and she wears absorbent pads. She has occasional urinary incontinence when she coughs or sneezes. There is no history of gastrointestinal or rectal surgery and no neurologic symptoms. Examination reveals no perianal deformity or rectal prolapse. The tone of the anal canal is adequate, whereas contractions of the anal sphincter and puborectalis muscles are weak. When the patient bears down, there is no rectal prolapse, and perineal descent is approximately 2 cm. How should she be evaluated and treated?

See P. 1648; CME, P. 1693

A 56-Year-Old Woman with Renal Failure after Heart–Lung Transplantation

A 56-year-old woman was admitted to the hospital because of renal failure. Ten years earlier, heart–lung transplantation had been performed because of primary pulmonary hypertension; her immunosuppressive regimen consisted of cyclosporine, prednisone, and azathioprine. Her medical history included glomerulonephritis at the age of 19 years, which resolved, and recurrent urinary tract infections. Renal function had been deteriorating slowly since the transplantation, and proteinuria had developed. A diagnostic procedure was performed.

See P. 1657; CME, P. 1694

The Decrease in Breast-Cancer Incidence in 2003 in the United States

Analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries shows that the age-adjusted incidence of breast cancer in the United States fell sharply by 6.7% in 2003, as compared with the rate in 2002. The decrease began in mid-2002 and had begun to level off by mid-2003. The authors attribute the decline to a sharp drop in the use of postmenopausal hormone-replacement therapy.

See P. 1670
Transfusion Strategies for Patients in Pediatric Intensive Care Units

Jacques Lacroix, M.D., Paul C. Hébert, M.D., James S. Hutchison, M.D., Heather A. Hume, M.D., Marisa Tucci, M.D., Thierry Ducruet, M.Sc., France Gauvin, M.D., Jean-Paul Collet, M.D., Ph.D., Baruch J. Toledano, M.D., Pierre Robillard, M.D., Ari Joffe, M.D., Dominique Biarent, M.D., Kathleen Meert, M.D., and Mark J. Peters, M.D., for the TRIPICU Investigators,* the Canadian Critical Care Trials Group, and the Pediatric Acute Lung Injury and Sepsis Investigators Network

ABSTRACT

From Université de Montréal (J.L., H.A.H., M.T., T.D., F.G., B.J.T.) and McGill University (P.R.) — both in Montreal; University of Ottawa, Ottawa (P.C.H.); University of Toronto, Toronto (J.S.H.); University of British Columbia, Vancouver (J.-P.C.); and University of Alberta, Edmonton (A.J.) — all in Canada; Université Libre de Bruxelles, Brussels (D.B.); Wayne State University, Detroit (K.M.); and the Institute of Child Health, London (M.J.P.). Address reprint requests to Dr. Lacroix at the Sainte-Justine Hospital, Rm. 3431, 3175 Côte Sainte-Catherine, Montreal, QC H3T 1C5, Canada, or at jacques_lacroix@ssss.gouv.qc.ca.

*Investigators and site investigators of the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) Study are listed in the Appendix.


BACKGROUND

The optimal hemoglobin threshold for erythrocyte transfusions in critically ill children is unknown. We hypothesized that a restrictive transfusion strategy of using packed red cells that were leukocyte-reduced before storage would be as safe as a liberal transfusion strategy, as judged by the outcome of multiple-organ dysfunction.

METHODS

In this noninferiority trial, we enrolled 637 stable, critically ill children who had hemoglobin concentrations below 9.5 g per deciliter within 7 days after admission to an intensive care unit. We randomly assigned 320 patients to a hemoglobin threshold of 7 g per deciliter for red-cell transfusion (restrictive-strategy group) and 317 patients to a threshold of 9.5 g per deciliter (liberal-strategy group).

RESULTS

Hemoglobin concentrations were maintained at a mean (±SD) level that was 2.1±0.2 g per deciliter lower in the restrictive-strategy group than in the liberal-strategy group (lowest average levels, 8.7±0.4 and 10.8±0.5 g per deciliter, respectively; P<0.001). Patients in the restrictive-strategy group received 44% fewer transfusions; 174 patients (54%) in that group did not receive any transfusions, as compared with 7 patients (2%) in the liberal-strategy group (P<0.001). New or progressive multiple-organ dysfunction syndrome (the primary outcome) developed in 38 patients in the restrictive-strategy group, as compared with 39 in the liberal-strategy group (12% in both groups) (absolute risk reduction with the restrictive strategy, 0.4%; 95% confidence interval, –4.6 to 5.4). There were 14 deaths in each group within 28 days after randomization. No significant differences were found in other outcomes, including adverse events.

CONCLUSIONS

In stable, critically ill children a hemoglobin threshold of 7 g per deciliter for red-cell transfusion can decrease transfusion requirements without increasing adverse outcomes. (Controlled-trials.com number, ISRCTN37246456.)
Up to 50% of children who are hospitalized in an intensive care unit (ICU) receive red-cell transfusions,\textsuperscript{1,2} yet children whose condition is stable may tolerate the decreased oxygen delivery associated with a moderate degree of anemia. On the one hand, transfusions containing leukocytes could have limited benefit in such children and might result in organ dysfunction through stimulation of the inflammatory cascade by the transfused leukocytes.\textsuperscript{3} On the other hand, children in the ICU could benefit from transfusions because of enhanced oxygen delivery, just as adults with early septic shock benefit from transfusions.\textsuperscript{4}

A randomized trial involving 838 critically ill adults suggested that a restrictive transfusion strategy may be superior to a liberal strategy.\textsuperscript{5} There are no data from rigorous trials to guide transfusion decisions in critically ill children. Several surveys of pediatric intensivists have recently documented large variations in stated\textsuperscript{6,7} and observed\textsuperscript{1,2} practices with respect to red-cell transfusion.

Universal leukocyte reduction, recently introduced in many countries, may decrease the pro-inflammatory effects of transfusions.\textsuperscript{8} We postulated that a restrictive transfusion strategy with the use of prestorage leukocyte-reduced red-cell units (i.e., red cells that have first been filtered to remove leukocytes and have then been stored in the usual manner) in stable, critically ill children would substantially decrease exposure to transfusions without worsening organ dysfunction.

\textbf{METHODS}

\textbf{PATIENTS AND SITES}

We enrolled patients at 19 tertiary-care pediatric ICUs in four countries (see the Appendix). Stable, critically ill children between 3 days and 14 years of age who had at least one hemoglobin concentration of 9.5 g per deciliter or less within the first 7 days after admission to the pediatric ICU were eligible for enrollment. The condition of patients was considered stable if the mean systemic arterial pressure was not less than 2 SD below the normal mean for age and if cardiovascular treatments had not been increased for at least 2 hours before enrollment. All consecutive children were screened. Exclusion criteria are listed in Figure 1. The study protocol was approved by the research ethics board at each participating institution, and for all patients, written informed consent was obtained from a parent or surrogate decision maker.

\textbf{STUDY DESIGN AND TREATMENT PROTOCOLS}

Randomization was centralized, with assignment data posted on the Internet. Patients were assigned to the study groups in blocks of 2 or 4 that were randomly distributed and stratified according to center and three age groups (≤28 days, 29 to 364 days, and >364 days). Physicians, nurses, and research staff were unaware of the block-randomization strategy.

In the restrictive-strategy group, the hemoglobin threshold for transfusion was set at 7 g per deciliter, with a target range after transfusion of 8.5 to 9.5 g per deciliter. In the liberal-strategy group, the threshold was 9.5 g per deciliter, with a target range of 11 to 12 g per deciliter. In both groups, red cells were transfused within 12 hours after the threshold value had been reached. Red-cell transfusions were administered in accordance with a formula that accounted for the patient’s weight and the average hemoglobin concentration in red-cell units at each participating site. Only prestorage leukocyte-reduced red-cell units were used.

Attending physicians followed strategies for red-cell transfusion outlined for each group. No other clinical care protocols were used in the study. The transfusion protocol was applied for up to 28 days of the stay in the pediatric ICU or until the time of death, whichever occurred first. The protocol could be temporarily suspended, at the discretion of the attending physician, during periods of active and clinically significant blood loss, surgical intervention, severe hypoxemia, or hemodynamic instability and was promptly resumed once the condition of the patient no longer fulfilled the suspension criteria. Suspensions were not considered a breach of adherence to the protocol. Data monitoring and collection were unchanged during suspension. Clinical staff and parents were aware of the assignments to study groups, but the statistician and members of the data and safety monitoring committee were unaware of the assignments.

\textbf{BASELINE ASSESSMENT, MONITORING, AND OUTCOME MEASURES}

Baseline assessments were undertaken at the time of randomization. Hemoglobin concentrations, the number of red-cell transfusions, the types of med-
5399 Patients were evaluated (hemoglobin ≤9.5 g/dl during first 7 days in pediatric ICU)

4372 Were excluded
1686 Were expected to stay <24 hr in ICU
424 Had no approval from physician
414 Were <3 days or >14 yr of age
216 Were unstable hemodynamically
201 Had acute blood loss
138 Weighed <3.0 kg
134 Had cardiovascular problems
115 Were never discharged from neonatal ICU
110 Had hemolytic anemia
75 Enrolled in another study

1027 Were screened for consent

379 Did not have consent provided by parent or surrogate decision maker

648 Underwent randomization

327 Patients were assigned to restrictive-strategy group

321 Patients were assigned to liberal-strategy group

7 Were withdrawn

320 Were included in intention-to-treat analysis

1 Had protocol violation

319 Were included in per-protocol analysis

307 Were included in per-protocol analysis

4 Were withdrawn

317 Were included in intention-to-treat analysis

10 Had protocol violation

Figure 1. Enrollment and Outcomes.

Some patients in pediatric intensive care units (ICUs) had more than one exclusion criterion. In addition to the causes listed for exclusion, other causes were a postconception age of less than 40 weeks (69 patients), severe thrombocytopenia (68), hypoxemia (65), a decision to withhold or withdraw critical care (59), predicted survival of less than 24 hours (54), previous enrollment in the study (33), brain death (25), extracorporeal membrane oxygenation (22), hemofiltration (21), blood exchange transfusion (20), plasmapheresis (17), an inability to receive blood products (14), and pregnancy (1). Among the 11 patients who were withdrawn from the intention-to-treat analysis, data were missing for 3 patients and could not be validated for 8 patients. Eleven patients were excluded from the per-protocol analysis because their hemoglobin level was below the threshold level during more than 20% of their stay after the first post-randomization day — our definition of noncompliance.
ications given, the use of mechanical ventilation and dialysis, and surgical interventions were recorded daily during the 28-day follow-up period. Hemoglobin concentrations were measured at least once within 6 hours after every red-cell transfusion. Data were collected by trained study personnel.

The primary outcome was the proportion of patients who died during the 28 days after randomization, had concurrent dysfunction of two or more organ systems (termed multiple-organ-dysfunction syndrome, or MODS), or had progression of MODS, as evidenced by the worsening of one or more organ dysfunctions, as defined by Proulx et al.9 We also collected information on a number of secondary outcomes, including daily scores on Paediatric Logistic Organ Dysfunction (PELOD) assessment,10 sepsis,9 transfusion reactions,11 nosocomial respiratory infections,12 catheter-related infections,13 adverse events, length of stay in the ICU and hospital, and mortality. Established diagnostic criteria were used.9,11-13

STATISTICAL ANALYSIS
We estimated that we would need to enroll at least 626 children in order to detect an absolute reduction of 10 percent in the risk of new or progressive organ dysfunction in the group treated according to the restrictive transfusion strategy, with an overall one-sided alpha of 5% and a power of 90%.14,15

One planned interim safety analysis was undertaken by a blinded, independent data and safety monitoring board after 50% of patients had been enrolled. Only unexpected rates of death, adverse events, and nosocomial infections were considered, and no statistical analysis was done. The board recommended continuation of the trial.

We compared the two groups with respect to the total number of transfusions per patient and the proportion of patients who did not have red-cell transfusions after randomization. We used analysis of variance with repeated measures to highlight differences in hemoglobin concentrations over time. We then calculated the number needed to treat to prevent one red-cell transfusion in the restrictive group.

The statistical analysis of the primary outcome measure was conducted with the use of an intention-to-treat approach. We calculated the 95% confidence interval (CI) for the absolute risk reduction16 in the proportion of patients with new or progressive MODS. We established a priori that we would infer that a restrictive strategy was not inferior to a liberal strategy for red-cell transfusions if the upper limit of the 95% CI for the absolute reduction in the risk of the primary outcome did not exceed a 10% margin of safety.17 We generated Kaplan–Meier curves and used the log-rank test to compare the time to the development of new or progressive organ failure in the two groups. We calculated adjusted odds ratios for treatment effects with the use of logistic regression; the multivariate model included age, country, and score on the Pediatric Risk of Mortality (PRISM) assessment.18 To minimize the probability of missing true differences, we also conducted a per-protocol analysis of the primary outcome in patients who met or exceeded an 80% rate of adherence to the protocol for red-cell transfusion. Adherence was defined as the proportion of days after randomization on which at least one hemoglobin concentration was over the transfusion threshold.

All analyses of secondary outcomes were based on the intention-to-treat principle. We compared daily PELOD scores, using the worst scores after baseline, the average total number of organs that were dysfunctional per patient, and other secondary outcomes listed above. Continuous variables were compared with the use of the Student t-test or the Wilcoxon rank-sum test. Categorical variables were analyzed with the use of the chi-square test.

We examined subgroups of patients who were at potential risk for adverse effects of anemia, categorized according to diagnosis, age, severity of illness (as estimated by the PRISM score), country, and study status (i.e., whether patients had been temporarily suspended from the trial).

Continuous data are expressed as means ±SD. We report two-sided 95% CIs and P values. No adjustments of P values were made for multiple comparisons. Data were analyzed with SAS software, version 9.1 (SAS Institute).

RESULTS

PATIENTS AND TREATMENT ASSIGNMENT
From November 26, 2001, to August 28, 2005, a total of 5399 children had a hemoglobin concentration of 9.5 g per deciliter or less during the first 7 days of admission to the ICU and were eligible for inclusion. Of these children, 4372 (81%) met at least one exclusion criterion (Fig. 1). For 379 of the remaining 1027 patients (37%), the parents or surrogate decision makers declined to provide consent. We therefore randomly assigned 648 children to
Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restrictive-Strategy Group (N=320)</th>
<th>Liberal-Strategy Group (N=317)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On admission to pediatric ICU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — mo</td>
<td>35.8±6.2</td>
<td>39.6±6.9</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>14.0±14.8</td>
<td>15.1±15.3</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>190 (59)</td>
<td>191 (60)</td>
</tr>
<tr>
<td>PRISM score†</td>
<td>9.4±6.7</td>
<td>9.1±6.7</td>
</tr>
<tr>
<td>Mechanical ventilation — no. (%)‡</td>
<td>253 (79)</td>
<td>252 (79)</td>
</tr>
<tr>
<td><strong>Red-cell transfusions before randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients — no. (%)</td>
<td>45 (14)</td>
<td>59 (19)</td>
</tr>
<tr>
<td>Volume of transfusions per transfused patient — ml/kg</td>
<td>16.9±11.8</td>
<td>14.7±10.7</td>
</tr>
<tr>
<td>No. of red-cell units per transfused patient</td>
<td>1.4±0.8</td>
<td>1.3±0.9</td>
</tr>
<tr>
<td>Length of storage of red-cell units — days</td>
<td>14.9±11.8</td>
<td>15.2±10.6</td>
</tr>
<tr>
<td><strong>Day of randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin — g/dl</td>
<td>8.0±1.0</td>
<td>8.0±0.9</td>
</tr>
<tr>
<td>Length of stay in ICU — days</td>
<td>2.3±1.7</td>
<td>2.3±1.8</td>
</tr>
<tr>
<td>Age — no. (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤28 days</td>
<td>11 (3)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>29–364 days</td>
<td>143 (45)</td>
<td>142 (45)</td>
</tr>
<tr>
<td>&gt;364 days</td>
<td>166 (52)</td>
<td>167 (53)</td>
</tr>
<tr>
<td>Country — no. (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium (3 sites)</td>
<td>66 (21)</td>
<td>66 (21)</td>
</tr>
<tr>
<td>Canada (10 sites)</td>
<td>205 (64)</td>
<td>203 (64)</td>
</tr>
<tr>
<td>United Kingdom (3 sites)</td>
<td>26 (8)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>United States (3 sites)</td>
<td>23 (7)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Surgery — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>63 (20)</td>
<td>62 (20)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>15 (5)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Other surgery or transplantation</td>
<td>45 (14)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Severity of illness (PRISM score)†</td>
<td>4.8±4.4</td>
<td>4.8±4.3</td>
</tr>
<tr>
<td>Septic state — no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome</td>
<td>157 (49)</td>
<td>155 (49)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>67 (21)</td>
<td>66 (21)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>31 (10)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>13 (4)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Multiple-organ-dysfunction syndrome — no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory dysfunction</td>
<td>234 (73)</td>
<td>246 (78)</td>
</tr>
<tr>
<td>Cardiovascular dysfunction</td>
<td>76 (24)</td>
<td>75 (24)</td>
</tr>
<tr>
<td>Hematologic dysfunction</td>
<td>42 (13)</td>
<td>39 (12)</td>
</tr>
<tr>
<td>Neurologic dysfunction</td>
<td>22 (7)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>7 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Gastrointestinal dysfunction</td>
<td>7 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>9 (3)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>PELOD score (day 1)‖</td>
<td>6.3±6.8</td>
<td>5.2±6.2</td>
</tr>
<tr>
<td>No. of dysfunctional organs (day 1)</td>
<td>1.3±0.9</td>
<td>1.3±0.8</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
† Scores on the Pediatric Risk of Mortality (PRISM) assessment range from 0 to 76, with higher scores indicating a greater risk of death.
‡ Patients underwent either invasive or noninvasive mechanical ventilation.
§ Randomization was performed in blocks according to center and age.
¶ Organ dysfunction was determined as defined by Proulx et al.9
‖ Scores on the Paediatric Logistic Organ Dysfunction (PELOD) assessment range from 0 to 71, with higher scores indicating more severe organ dysfunction.
the two study groups. Of those, 11 (2%) were withdrawn after randomization, leaving 637 patients (320 in the restrictive-strategy group and 317 in the liberal-strategy group) in the intention-to-treat analyses. Patients in the two study groups had similar characteristics at baseline (Table 1).

**Table 2. Red-Cell Transfusions, Temporary Protocol Suspensions, and Cointerventions.**

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Red-cell transfusion and hemoglobin concentration after randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No red-cell transfusion — no. of patients (%)</td>
<td>174 (54)</td>
<td>7 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of red-cell units per patient</td>
<td>0.9±2.6</td>
<td>1.7±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest hemoglobin level in ICU — g/dl†</td>
<td>8.7±0.4</td>
<td>10.8±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients undergoing red-cell transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any transfusion — no. of patients (%)</td>
<td>146 (46)</td>
<td>310 (98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 transfusion — no. of patients (%)</td>
<td>104 (32)</td>
<td>194 (61)</td>
<td></td>
</tr>
<tr>
<td>2 transfusions — no. of patients (%)</td>
<td>18 (6)</td>
<td>82 (26)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 transfusions — no. of patients (%)</td>
<td>24 (8)</td>
<td>34 (11)</td>
<td></td>
</tr>
<tr>
<td>No. of red-cell units per transfused patient</td>
<td>1.9±3.4</td>
<td>1.7±2.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Volume of red-cell units per transfused patient — ml/kg</td>
<td>23.6±52.5</td>
<td>20.0±19.3</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>First red-cell transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from randomization to first transfusion — days</td>
<td>1.7</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin level — g/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before first transfusion</td>
<td>6.7±0.5</td>
<td>8.1±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After first transfusion</td>
<td>9.4±1.2</td>
<td>11.2±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All red-cell transfusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of transfusions‡</td>
<td>301</td>
<td>542</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average length of storage — days</td>
<td>16.0±10.5</td>
<td>15.7±10.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Adherence to threshold hemoglobin level — no. of patients (%)§</td>
<td>319 (100)</td>
<td>307 (97)</td>
<td>0.006</td>
</tr>
<tr>
<td>Temporary suspension of research protocol¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients — no. (%)</td>
<td>39 (12)</td>
<td>20 (6)</td>
<td>0.01</td>
</tr>
<tr>
<td>PRISM score at randomization</td>
<td>6.5±4.8</td>
<td>7.2±5.2</td>
<td>0.63</td>
</tr>
<tr>
<td>Transfusion during suspension — no. of patients (%)</td>
<td>36 (11)</td>
<td>11 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of transfusions during suspension‡</td>
<td>71</td>
<td>61</td>
<td>0.41</td>
</tr>
<tr>
<td>Reason for suspension — no. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome with hypoxemia</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute blood loss</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hemofiltration primed with red cells</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Length of suspension — days‖</td>
<td>3.3±5.2</td>
<td>1.9±1.6</td>
<td>0.85</td>
</tr>
</tbody>
</table>

**INTERVENTION**

Hemoglobin concentrations at the time of randomization were similar in the restrictive-strategy group and the liberal-strategy group (8.0±1.0 vs. 8.0±0.9 g per deciliter). There were significant differences between the groups in the time until the first trans-
fusion (1.7 vs. 0.1 days) and in the hemoglobin concentration before the first transfusion (6.7±0.5 vs. 8.1±0.1 g per deciliter) (P<0.001 for both comparisons) (Table 2). The hemoglobin concentrations were maintained above the threshold more than 94% of the time, with an average difference of 2.1±0.2 g per deciliter between the restrictive-strategy group and the liberal-strategy group (overall average lowest levels, 8.7±0.4 and 10.8±0.5 g per deciliter, respectively) until discharge from the pediatric ICU (P<0.001) (Fig. 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The protocol was temporarily suspended for 59 patients: 39 in the restrictive-strategy group and 20 in the liberal-strategy group (Table 2). Overall, 301 transfusions were administered in the restrictive-strategy group, as compared with 542 in the liberal-strategy group (a 44% decrease in the restrictive-strategy group and 61 in the liberal-strategy group were given while patients were suspended from the study. One patient in the liberal-strategy group received 29 transfusions during study suspension. Attending physicians were permitted to transfuse more red cells than indicated in the study protocol if one of the following events occurred: severe acute respiratory distress syndrome with refractory hypoxemia; shock; instability in the patient’s condition; acute blood loss; surgery; blood exchange-transfusion (manual or automated); hemofiltration, if priming was done with blood; or extracorporeal membrane oxygenation or plasmapheresis.

It was expected that red cells would be transfused if the hemoglobin concentration fell below 7 g per deciliter in the restrictive-strategy group or below 9.5 g per deciliter in the liberal-strategy group.

Attending physicians were permitted to transfuse more red cells than indicated in the study protocol if one of the following events occurred: severe acute respiratory distress syndrome with refractory hypoxemia; shock; instability in the patient’s condition; acute blood loss; surgery; blood exchange-transfusion (manual or automated); hemofiltration, if priming was done with blood; or extracorporeal membrane oxygenation or plasmapheresis.

The median length of suspension was 1 day in both groups.

** Agents included dobutamine, dopamine (at least 5 μg per kilogram of body weight per minute), epinephrine, milrinone, nitroglycerin, nitroprusside, norepinephrine, phenylephrine, and vasopressin.

### Table 2. (Continued.)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Cointerventions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh-frozen plasma — no. (%)</td>
<td>23 (7)</td>
<td>25 (8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Platelets — no. (%)</td>
<td>26 (8)</td>
<td>29 (9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Albumin — no. (%)</td>
<td>90 (28)</td>
<td>81 (26)</td>
<td>0.46</td>
</tr>
<tr>
<td>Corticosteroids — no. (%)</td>
<td>107 (33)</td>
<td>124 (39)</td>
<td>0.12</td>
</tr>
<tr>
<td>Administration of fluid (intake minus output) — ml/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On first day</td>
<td>15.8±35.5</td>
<td>21.3±38.5</td>
<td>0.06</td>
</tr>
<tr>
<td>During stay in ICU</td>
<td>119±236</td>
<td>100±177</td>
<td>0.27</td>
</tr>
<tr>
<td>Vasoactive drugs — no. (%)**</td>
<td>106 (33)</td>
<td>99 (31)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.

† The average difference between the restrictive-strategy group and the liberal-strategy group was 2.1±0.2 g per deciliter from randomization to discharge from the pediatric ICU.

‡ The number is for all transfusions after randomization, including those given during suspension; 71 transfusions in the restrictive-strategy group and 61 in the liberal-strategy group were given while patients were suspended from the study. One patient in the liberal-strategy group received 29 transfusions during study suspension.

§ It was expected that red cells would be transfused if the hemoglobin concentration fell below 7 g per deciliter in the restrictive-strategy group or below 9.5 g per deciliter in the liberal-strategy group.

¶ Attending physicians were permitted to transfuse more red cells than indicated in the study protocol if one of the following events occurred: severe acute respiratory distress syndrome with refractory hypoxemia; shock; instability in the patient’s condition; acute blood loss; surgery; blood exchange-transfusion (manual or automated); hemofiltration, if priming was done with blood; or extracorporeal membrane oxygenation or plasmapheresis.

‖ The median length of suspension was 1 day in both groups.

** Agents included dobutamine, dopamine (at least 5 μg per kilogram of body weight per minute), epinephrine, milrinone, nitroglycerin, nitroprusside, norepinephrine, phenylephrine, and vasopressin.

### PRIMARY OUTCOME

The number of patients with new or progressive MODS after randomization was 38 in the restrictive-strategy group and 39 in the liberal-strategy group (12% of both groups). The absolute reduction in risk was 0.4% (95% CI, –4.6 to 5.5 with the restrictive strategy); the upper limit of the 95% CI did not exceed 10%.

The risk of new or progressive MODS increased with the severity of illness, as reflected by the PRISM score, in both groups (Table 3). The time-to-event analysis for new or progressive MODS generated a hazard ratio of 0.95 for the restrictive transfusion strategy as compared with the liberal strategy (95% CI, 0.61 to 1.49; P=0.84).
None of the measures of the severity of organ dysfunction differed significantly between the two groups (Table 3). The number of deaths 28 days after randomization was the same in the two groups (14). No significant differences were observed with respect to nosocomial infections, mechanical ventilation, the duration of the stay in the ICU, or reactions to red-cell transfusion. There were 221 adverse events in the restrictive-strategy group and 203 in the liberal-strategy group ($P = 0.44$); of those events, 28 and 22, respectively, were serious adverse events ($P = 0.42$). Patients with one or more adverse events included 97 in the restrictive-strategy group and 90 in the liberal-strategy group ($P = 0.59$), and 19 patients in each group had one or more serious adverse events ($P = 0.98$). A complete list of adverse events can be found in the Supplementary Appendix.

We also performed a per-protocol analysis of the primary outcome. A total of nearly 99% of patients met the 80% adherence criterion, and the results of the per-protocol analysis differed only slightly from those of the intention-to-treat analysis (absolute risk reduction with the restrictive strategy, 0.8%; 95% CI, –4.3 to 5.9).

**DISCUSSION**

We found that as compared with a liberal transfusion strategy, a restrictive strategy with a hemoglobin threshold of 7 g per deciliter resulted in a
96% reduction in the number of patients who had any transfusion exposure and a 44% decrease in the number of red-cell transfusions administered, without increasing the rates of new or progressive MODS, in stable, critically ill children. There were also no clinically important differences between the two groups in any secondary outcomes.

Our study showed that a restrictive transfusion strategy was safe in pediatric patients whose condition was stable in the ICU and that such a strategy was as safe as a liberal transfusion strategy. However, outcomes in critically ill adults differ from our findings in children. In a trial of two transfusion strategies in critically ill adults, the rates of worsening organ failure and other complications were significantly higher with a liberal transfusion strategy. This study in adults also documented more in-hospital deaths in the liberal-strategy group than in the restrictive-strategy group, whereas the number of deaths was the same with the two strategies in our pediatric patients (14 in each group).

The differences between our results and those in adults may be due to several factors. First, critically ill adults may be more vulnerable than critically ill children to adverse consequences of red-cell transfusions. Second, the trial in adults did not use prestorage leukocyte-reduced red cells, as were used in our trial. Leukocytes in transfused red cells may harm vulnerable patients by generating cytokines and activating an inflammatory response. Two randomized trials involving adults who had vascular disease or who had undergone cardiac surgery showed decreased rates of organ dysfunction in patients receiving leukocyte-reduced red cells. In addition, two before-and-after trials that evaluated a universal prestorage leukocyte-reduction program showed reduced rates of febrile episodes among more than 14,000 adults and decreased rates of post-transfusion bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis in premature infants. Hence, in our study, prestorage leukocyte reduction may have helped prevent harmful

Table 3. (Continued.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restrictive-Strategy Group</th>
<th>Liberal-Strategy Group</th>
<th>Absolute Risk Reduction, Odds Ratio, or Difference in Means (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ICU</td>
<td>11/320 (3)</td>
<td>8/317 (3)</td>
<td>–0.9 (–3.6 to 1.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>From any cause during 28-day study</td>
<td>14/320 (4)</td>
<td>14/317 (4)</td>
<td>0 (–3.2 to 3.2)</td>
<td>0.98</td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>65/320 (20)</td>
<td>79/317 (25)</td>
<td>4.6 (–1.9 to 11.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>At least 1 adverse event</td>
<td>97/320 (30)</td>
<td>90/317 (28)</td>
<td>–1.92 (–9.0 to 5.2)</td>
<td>0.59</td>
</tr>
<tr>
<td>Reactions to red-cell transfusion</td>
<td>3/320 (1)</td>
<td>6/317 (2)</td>
<td>1.0 (–0.9 to 2.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>Duration of care—days</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6.2±5.9</td>
<td>6.0±5.4</td>
<td>–0.14 (–1.1 to 0.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>ICU stay after randomization</td>
<td>9.5±7.9</td>
<td>9.9±7.4</td>
<td>0.46 (–0.7 to 1.7)</td>
<td>0.39</td>
</tr>
</tbody>
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* Plus–minus values are means ±SD.
† The comparison between the restrictive-strategy group and the liberal-strategy group is given as an absolute reduction in risk.
‡ Noninferiority (NI) was checked only for the primary outcome (the number of patients who had new or progressive multiple-organ-dysfunction syndrome [MODS], including death, after randomization). The absolute risk reduction for new or progressive MODS in the restrictive-strategy group versus the liberal-strategy group was 0.4% (two-sided 95% CI, –4.6 to 5.5) by intention-to-treat analysis; we also calculated a two-sided 97.5% CI of –5.4 to 6.2. Some experts also consider that a per-protocol analysis should be done in a noninferiority trial. In the per-protocol analysis, we excluded 11 patients who did not meet the 80% adherence criterion; the number of patients with the primary outcome was 37 of 319 (11.6%) in the restrictive-strategy group and 38 of 307 (12.4%) in the liberal-strategy group (absolute risk reduction, 0.8%; two-sided 95% CI, –4.3 to 5.9). In all analyses, the upper limit of the confidence interval was lower than the safety margin of error of 10% approved by consensus before the study was undertaken, which means that noninferiority was statistically significant.
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§ The comparison between the restrictive-strategy group and the liberal-strategy group is given as an absolute reduction in risk.
** Scores on the Paediatric Risk of Mortality (PRISM) range from 0 to 76, with higher scores indicating a higher risk of death.
†† Scores on the Paediatric Logistic Organ Dysfunction (PELOD) assessment range from 0 to 71, with higher scores indicating more severe organ dysfunction. The PELOD score can be estimated over the entire stay in the ICU or over 1 day (daily PELOD). The change in the PELOD score is the difference between the daily PELOD score at study entry and the worst daily PELOD score thereafter. Patients whose PELOD score did not change or decreased after randomization were considered to have a change of 0.
effects of transfusions, especially in the liberal group.

Three smaller trials in pediatric subpopulations have also evaluated various transfusion strategies. In a trial involving 147 pediatric patients undergoing cardiac surgery, a hematocrit of 21% during cardiopulmonary bypass was associated with a poor neurodevelopmental outcome, as compared with a hematocrit of 27%. In a subgroup of patients in a study of 100 preterm infants who were randomly assigned to a restrictive or liberal transfusion strategy, the risk of intraparenchymal brain hemorrhage, periventricular leukomalacia, and apnea was higher in the restrictive-strategy group. In a trial that included 451 premature infants who were randomly assigned to a restrictive or liberal transfusion strategy, the rate of death or severe morbidity was 2.6 percentage points higher in the restrictive-strategy group, but the difference was not significant. From published reports, it is unclear whether red cells underwent prestorage leukocyte reduction in these three pediatric trials.

To minimize potential biases, we concealed treatment assignments, ensured complete follow-up, and assessed objective clinical outcomes. We lost only 11 patients to follow-up (2%), a rate low enough to prevent any bias attributable to samplesize slippage. Despite varying practice patterns before this study, the adherence rates in the many participating centers exceeded 97% in both groups. Inferences related to clinical outcomes derived from this study are strengthened by the consistency of observations in both primary and secondary outcomes and across major subgroups. We did note that in the restrictive-strategy group, there were significantly more suspensions of the transfusion-threshold protocol, which may reflect the uneasiness of attending physicians about maintaining very sick patients at low hemoglobin concentrations. Suspensions were a result of the acute respiratory distress syndrome, worsened shock, or increased bleeding but did not cause these complications. Despite the increased number of suspensions, we nevertheless documented a significant reduction in the number of red-cell units transfused in the restrictive group.

Our trial had at least one limitation. Although death is the reference outcome in studies of critically ill adults, the low mortality rate among children — only about 4% — would not allow us to design a study with sufficient power to detect a meaningful change in death rates. In critical care medicine, organ failure is a clinically significant outcome. We used a composite of death and development of new or progressive organ failure, which should be relevant to pediatric intensivists.

In conclusion, we found that a restrictive transfusion strategy can safely decrease the rate of exposure to red cells as well as the total number of transfusions in critically ill children, even though suspensions of transfusion strategies were permitted under prespecified conditions. We were unable to detect meaningful differences in any clinical outcomes, both overall and among all subgroups examined. We recommend a restrictive transfusion strategy in pediatric patients whose condition is stable in the ICU. This recommendation, however, is not applicable to premature infants, older adults, patients with coronary artery disease, or children with severe hypoxemia, hemodynamic instability, active blood loss, or cyanotic heart disease.

Supported by grants (84300 and 130770) from the Canadian Institutes of Health Research and by grants (3348 and 3568) from the Fonds de la Recherche en Santé du Québec. Drs. Lacroix and Hébert report receiving consulting fees and grant support from Johnson & Johnson; Dr. Hébert also reports receiving consulting fees and unrestricted funds from Novo Nordisk and Amgen serving as a Career Scientist of the Ontario Ministry of Health (1994–2004), and receiving unrestricted training funds from Canadian Blood Services; Dr. Hume reports being employed by the Canadian Blood Services; and Dr. Peters reports receiving consulting fees from Baxter, Koma, and Eli Lilly. No other potential conflict of interest relevant to this article was reported.

We thank the children who participated in this trial and their families; Scott Bateman, John Marshall, Maureen Meade, Adrienne Randolph, Tasmin Sinuff, and Scott Watson for their comments and support; Jean-Pierre Le Cruguel for his help with the statistical analysis; David Paquin for database management; and Ann Robinson for her work as a study monitor.

APPENDIX

The following investigators participated in this study: Executive Committee: J. Lacroix (chair), P.C. Hébert, J.S. Hutchison, H.A. Hume, M. Tucci, F. Gauvin, J.P. Collet, B.J. Toledano, P. Robillard, and T. Ducruet. Data Safety and Monitoring Board: G.É. Rivard (committee chair, hematologist, Sainte-Justine Hospital), J.P. Collet (trial methodologist, McGill University), M.C. Guertin (biostatistician, Institut de Cardiologie de Montréal), C. Litalien (pediatric intensivist, Sainte-Justine Hospital), D.J. Cook (chair of the Canadian Critical Care Trials Group, trial methodologist and intensivist, McMaster University), and A. Proietti (trial manager, ex officio). Data Management Committee: J. Lacroix (chair), T. Ducruet (biostatistician), D. Paquin (database coordinator), and A. Proietti (trial manager, ex officio). Study Managers: A. Proietti, D. David, and R. Trahan. Institutions and Site Investigators (the number of study patients is given in parentheses).

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British Columbia Children’s Hospital, Vancouver (47) — P. Skippen, D. Wensley; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC (11) — C. Cy; Children’s Hospital of Eastern Ontario, Ottawa (41) — D. Creery, H. Writer; Children’s Hospital of Western Ontario, London (6) — Y. Ouellette; Hamilton Health Science Corporation, Hamilton, ON (26) — K. Choong, H. Kirpalani; Hospital for Sick Children, Toronto (76) — J.S. Hutchinson; Kingston General Hospital, Kingston, ON (12) — E. Tsai; Montreal Children’s Hospital, Montreal (33) — R. Gottsmann; Sainte-Justine Hospital, Montreal (67) — F. Gauvin. United Kingdom: Birmingham Children’s Hospital, Birmingham (13) — K. Morris; Great Ormond Street Hospital for Children, London (28) — M.J. Peters; Queen’s Medical Centre, Nottingham (8) — H. Vyas. United States: Children’s Hospital of Michigan, Detroit (33) — K. Meert; University of Virginia Children’s Hospital Center, Charlottesville (2) — D. Willson. Writing Committee: J. Lacroix (chair), members of the Executive Committee, A. Joffe, D. Biarent, K. Meert, M.J. Peters, and site investigators.

REFERENCES

Effect of Torcetrapib on Carotid Atherosclerosis in Familial Hypercholesterolemia

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Drs. Kastelein and Bots contributed equally to this article.

*Investigators and committees of the Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE 1) trial are listed in the Appendix.

This article (10.1056/NEJMoa071359) was published at www.nejm.org on March 26, 2007.


Background
Torcetrapib, an inhibitor of cholesteryl ester transfer protein, may reduce atherosclerotic vascular disease by increasing levels of high-density lipoprotein (HDL) cholesterol.

Methods
A total of 850 patients with heterozygous familial hypercholesterolemia underwent B-mode ultrasonography at baseline and at follow-up to measure changes in carotid intima–media thickness. The patients completed an atorvastatin run-in period and were subsequently randomly assigned to receive either atorvastatin monotherapy or atorvastatin combined with 60 mg of torcetrapib for 2 years.

Results
After 24 months, in the atorvastatin-only group, the mean (±SD) HDL cholesterol level was 52.4±13.5 mg per deciliter and the mean low-density lipoprotein (LDL) cholesterol level was 143.2±42.2 mg per deciliter, as compared with 81.5±22.6 mg per deciliter and 115.1±48.5 mg per deciliter, respectively, in the torcetrapib–atorvastatin group. During the study, average systolic blood pressure increased by 2.8 mm Hg in the torcetrapib–atorvastatin group, as compared with the atorvastatin-only group. The increase in maximum carotid intima–media thickness, the primary measure of efficacy, was 0.0053±0.0028 mm per year in the atorvastatin-only group and 0.0047±0.0028 mm per year in the torcetrapib–atorvastatin group (P=0.87). The secondary efficacy measure, annualized change in mean carotid intima–media thickness for the common carotid artery, indicated a decrease of 0.0014 mm per year in the atorvastatin-only group, as compared with an increase of 0.0038 mm per year in the torcetrapib–atorvastatin group (P=0.005).

Conclusions
In patients with familial hypercholesterolemia, the use of torcetrapib with atorvastatin, as compared with atorvastatin alone, did not result in further reduction of progression of atherosclerosis, as assessed by a combined measure of carotid arterial-wall thickness, and was associated with progression of disease in the common carotid segment. These effects occurred despite a large increase in HDL cholesterol levels and a substantial decrease in levels of LDL cholesterol and triglycerides. (ClinicalTrials.gov number, NCT00136981.)
GUIDELINES FOR THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE FOCUS ON REDUCING LEVELS OF LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL BY MEANS OF HYDROXYMЕTHYLGLUTARYL COENZYME A (HMG-CoA) REDUCTASE INHIBITORS (COLLECTIVELY REFERRED TO AS STATINS). 

However, recent meta-analyses have shown that even with the most aggressive treatment, these drugs reduce the risk of a major coronary event by only 30%. This finding, combined with an estimation that mortality from cardiovascular causes will increase worldwide by 90% by the year 2020, as compared with that in 1990, illustrates the need for new efficacious treatments. A review of four large, prospective epidemiologic studies has shown that an increase of 1 mg per deciliter (0.03 mmol per liter) in high-density lipoprotein (HDL) cholesterol was associated with a 2 to 3% reduction in the risk of cardiovascular disease. Moreover, HDL cholesterol levels remain predictive of the risk of recurrent cardiovascular disease in patients who have reached LDL cholesterol levels below 70 mg per deciliter (1.8 mmol per liter) with intensive statin treatment.

During the past few years, attempts to raise HDL cholesterol levels have been particularly successful with small-molecule inhibitors of cholesteryl ester transfer protein (CETP). By blocking the CETP-mediated transfer of cholesteryl ester from HDL cholesterol to apolipoprotein-B–containing lipoproteins and the simultaneous transfer of triglycerides in the opposite direction, torcetrapib is very effective at raising HDL cholesterol levels. Indeed, elevated CETP levels were shown to be associated with an increased risk of future coronary artery disease in apparently healthy subjects. Furthermore, the inhibition of CETP in rabbit models of atherosclerosis dramatically reduced the extent of disease. It is not known, however, whether CETP inhibition attenuates atherosclerosis in humans. Since new lipid-modulating drugs will be primarily used in addition to evidence-based lowering of LDL cholesterol, torcetrapib has been developed for use in combination with atorvastatin. In this setting, torcetrapib not only increased levels of HDL cholesterol and apolipoprotein A-I but also decreased levels of LDL cholesterol and apolipoprotein B-100 (the latter especially at higher doses) and also showed favorable effects on increasing the size of both HDL and LDL particles.

In our study, we used a combination of torcetrapib and atorvastatin in patients with heterozygous familial hypercholesterolemia. The rationale for studying this target population was that mutations in the LDL-receptor gene are associated with decreased levels of HDL cholesterol, smaller HDL particle size, and increased levels of CETP. Also, the progression of atherosclerosis in familial hypercholesterolemia is related to levels of both HDL cholesterol and CETP. Therefore, it was hypothesized that the use of torcetrapib would have distinct favorable effects in this group of patients. The aim of our study was to evaluate the effects of torcetrapib on carotid intima–media thickness, a surrogate marker for end points of cardiovascular disease in patients with familial hypercholesterolemia.

The results of this study need to be considered in light of the recent discontinuation of the large Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial (ClinicalTrials.gov number, NCT00134264), which showed an increase in all-cause mortality associated with torcetrapib.

STUDY DESIGN

The Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE 1) trial was a prospective, double-blind, randomized, multicenter, parallel-group study. The trial was designed by the academic investigators in collaboration with the study sponsor. The institutional review board at each participating center approved the protocol, and patients provided written informed consent. Patients were eligible for entry into the study if they had received a diagnosis of heterozygous familial hypercholesterolemia either by genotyping or by having met the diagnostic criteria outlined by the World Health Organization.

During a run-in phase of 6 to 14 weeks, patients were counseled on therapeutic lifestyle changes and were administered atorvastatin at a dose of 20, 40, or 80 mg, titrated at 4-week intervals, for up to three visits to reach target LDL cholesterol levels, as recommended by guidelines from the National Cholesterol Education Program, or to reach the patient’s maximum tolerated dose. At study entry, patients who were taking cholesterol absorption inhibitors or bile-acid binders were permitted to continue taking these medications, provided that the dose was not changed during...
the course of the study. At the conclusion of the run-in period, patients were randomly assigned to receive either atorvastatin (at a dose established during the run-in period) with 60 mg of torcetrapib daily or atorvastatin monotherapy with corresponding placebo tablets. Patients and study personnel were unaware of study-group assignments, laboratory measurements, and carotid-imaging findings.

This article was written by the lead academic author, who vouches for the accuracy and completeness of the data and analyses. The study contract specified that a copy of the study database be provided to the coordinating center for independent analysis and granted the academic authors the unrestricted right to publish the results. The analyses have been confirmed by an independent center.
Carotid Ultrasonography

All patients underwent carotid ultrasonography to assess carotid intima–media thickness. Replicate scans were performed within a week of each other at baseline and at 24 months, with interim follow-up scans at 6, 12, and 18 months. At each visit, a circumferential scan was performed with image acquisition at four predefined angles of the near and far walls of the right and left common carotid artery, carotid bifurcation, and internal carotid...
artery. All imaging centers used the same imaging hardware, Sequoia 512 scanners equipped with 8L5 transducers (Siemens), and protocols for imaging acquisition. Five-second image sequences were saved in Digital Imaging in Communications in Medicine (DICOM) format (National Electrical Manufacturers Association) and were written to magnetic optical disks for transfer to reading centers. Two reading centers (at the University Medical Center in Utrecht, the Netherlands, and at Wake Forest University Medical Center in Winston-Salem, NC) used standardized equipment and protocols to process stored images.

Semiautomated readings were analyzed with the use of automated measurement software (Image and Data Analysis). From each image sequence, the reader selected one frame in end diastole for measurement of carotid intima–media thickness. The leading edge (far wall) and trailing edge (near wall) of boundaries between the media and adventitia and between the lumen and intima were traced within the region of interest specified by the reader. Maximum carotid intima–media thickness was determined from a set of measurements perpendicular to the media–adventitia boundary. The readers were unaware of study-group assignments and of previous measurements of carotid intima–media thickness when reading an image.

Quality-assurance processes included central training and certification of all sonographers and readers on each continent, annual international meetings of sonographers and readers to reinforce protocol and standardized implementation, and regular site visits and performance reviews. Intraclass correlation coefficients for the mean maximum carotid intima–media thickness between replicate scans at baseline for 875 patients and at the end of the study for 814 patients were 0.90 and 0.88, respectively. The intraclass correlation coefficient for the monthly quality-assurance scans for 128 patients was 0.96. These estimates include differences within and between visits, within and between sonographers, and within and between reader-variability components.

The primary end point was annualized change in the maximum carotid intima–media thickness for the 12 carotid-artery segments (near and far walls of the right and left common carotid artery, the carotid bifurcation, and the internal carotid artery) based on all scans performed during the 2-year study period.

**Statistical Analysis**

Three hundred four patients were needed in each treatment group for the study to have a power of 90% to detect a difference of 0.020 mm in the annualized rate of change of carotid intima–media thickness with a two-sided alpha level of 0.05, assuming a common standard deviation of 0.076 mm per year.

A linear mixed-effects model was used to analyze the annualized rate of change in maximum carotid intima–media thickness, including 84 maximum measurements (12 segments multiplied by 7 visits) for each patient as the dependent variables, with random intercepts and slopes as a function of time and fixed effects for geographic region, atorvastatin dose at run-in, carotid segment, treatment, time, and interaction between time and treatment. Testing was two-sided and conducted with a 5% type I error rate. Laboratory measurements were analyzed by analysis of covariance, including terms for baseline value, treatment, geographic region, and atorvastatin dose at run-in. Safety data were analyzed with the use of a linear model with terms for baseline value, hypertensive status, age, sex, race, smoking status, history of diabetes mellitus, body-mass index, creatinine clearance, and treatment.

With multiplicative interaction terms, we studied whether treatment effects differed across subgroups. These prespecified analyses were performed for age (<65 and ≥65 years), sex, race (white or nonwhite), HDL cholesterol levels (<40 mg and ≥40 mg per deciliter [1.0 mmol per liter]), LDL cholesterol levels (above and below the median), triglycerides (<150 mg and ≥150 mg per deciliter [1.7 mmol per liter]), smoking status, history of diabetes mellitus, history of hypertension, C-reactive protein levels (<3.0 mg and ≥3.0 mg per deciliter), and baseline maximum carotid intima–media thickness (above and below the median). Investigator-reported clinical adverse events were not tested for statistical differences because such events were not adjudicated and were expected to be low in frequency of occurrence. Therefore, the study did not have the power to detect differences.

**Results**

From December 19, 2003, to November 22, 2004, a total of 904 patients underwent randomization...
at 37 centers in North America, Europe, and South Africa. Of these patients, 454 were assigned to the atorvastatin-only group and 450 to the torcetrapib–atorvastatin group. A total of 850 patients (427 in the atorvastatin-only group and 423 in the torcetrapib–atorvastatin group) remained in the study and underwent ultrasonography of the carotid artery at least once both at baseline and at follow-up (the full-analysis set). (Details of study-group assignments appear in the Supplementary Appendix, which is available with the full text of this article at www.nejm.org.) Demographic characteristics and baseline medications were similar in the two study groups (Table 1). The titrated daily dose of atorvastatin averaged 56.5 mg in both groups.

**LABORATORY RESULTS AND BLOOD PRESSURE**

Table 1 summarizes laboratory values and blood pressure at baseline and during the study period for the 850 patients in the full-analysis set who had post-baseline ultrasonographic results that could be evaluated. After 24 months, mean HDL cholesterol levels increased from 51.8 to 52.4 mg per deciliter (1.3 to 1.4 mmol per liter) in the atorvastatin-only group and from 52.9 to 81.5 mg per deciliter (1.4 to 2.1 mmol per liter) in the torcetrapib–atorvastatin group (Fig. 1). In the atorvastatin-only group, mean LDL cholesterol levels measured 165.5 mg per deciliter (4.3 mmol per liter) at screening and fell during the run-in period to 138.9 mg per deciliter (3.6 mmol per liter) at baseline. After 24

![Figure 1](image)

**Figure 1.** Changes in Levels of High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) Cholesterol in Patients Receiving Atorvastatin Alone or Atorvastatin plus Torcetrapib.

Panels A and C show the levels of HDL and LDL cholesterol, respectively, in the study patients, and Panels B and D show the percent changes in HDL and LDL cholesterol, respectively, from baseline to 24 months, including a comparison of the percent change between the torcetrapib–atorvastatin group and the atorvastatin-only group for both HDL and LDL cholesterol (right-hand columns). To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
months of treatment, mean LDL cholesterol levels in the atorvastatin-only group were 143.2 mg per deciliter (3.7 mmol per liter). In the torcetrapib-atorvastatin group, mean LDL cholesterol levels were 168.2 mg per deciliter (4.3 mmol per liter) at screening, 138.4 mg per deciliter (3.6 mmol per liter) at baseline, and 115.1 mg per deciliter (3.0 mmol per liter) at 24 months. As compared with atorvastatin alone, the net effect of torcetrapib was a 51.9% relative increase in HDL cholesterol and a 20.6% relative decrease in LDL cholesterol. Table 2 shows changes in lipoprotein subclasses in the two study groups. Baseline blood pressure was 116/73 mm Hg in the torcetrapib–atorvastatin group and 117/74 mm Hg in the atorvastatin-only group. During the study, mean systolic blood pressure increased by 1.3 mm Hg in the atorvastatin-only group and by 4.1 mm Hg in the torcetrapib–atorvastatin group, a least-square mean difference of 2.8 mm Hg (95% confidence interval [CI], 1.9 to 3.7; P<0.001).

**CAROTID ULTRASONOGRAPHY**

Table 3 summarizes the change in the primary and secondary efficacy measures as seen on carotid ultrasonography. The primary efficacy measure, annualized rate of change in maximum carotid intima–media thickness, was an increase of 0.0053 mm per year in the atorvastatin-only group and an increase of 0.0047 mm per year in the torcetrapib–atorvastatin group (P=0.87) (Fig. 2). However, the secondary efficacy measure, annualized change in the maximum and mean measures of carotid intima–media thickness for the common carotid artery, indicated regression in the atorvastatin-only group (a maximum decrease of 0.0042 mm per year and a mean decrease of 0.0014 mm per year) and progression in the torcetrapib–atorvastatin group (a maximum increase of 0.0040 mm per year [P=0.02] and a mean increase of 0.0038 mm per year [P=0.005]) (Table 3).

For nearly all prespecified subgroups, no heterogeneity in the difference between study groups was observed. Annualized change in maximum carotid intima–media thickness in patients with a history of diabetes was lower in the torcetrapib–atorvastatin group than in the atorvastatin-only group (P=0.05), although the number of patients with diabetes was limited (9 in the torcetrapib–atorvastatin group and 17 in the atorvastatin-only group). For patients with baseline HDL cholesterol levels of less than 40 mg per deciliter (1.0 mmol per liter), the results showed a trend in favor of atorvastatin monotherapy (P=0.09). However both of these results are probably due to chance.

**DISCUSSION**

The RADIANCE 1 trial showed that the addition of torcetrapib to atorvastatin did not provide incremental halting of the progression of athero-...
sclerosis in the carotid arteries of patients with familial hypercholesterolemia, as has been previously shown with the use of atorvastatin alone. If anything, our data suggest a worsening of pathology conferred by this CETP inhibitor, despite a 52% increase in HDL cholesterol levels and a robust 21% decrease in LDL cholesterol levels in comparison with the results in the atorvastatin-only group. On the basis of extensive epidemiologic and various clinical-intervention studies, such lipoprotein changes were anticipated to render significant benefit.

To study atherosclerosis, we used ultrasonography to assess carotid intima–media thickness, a surrogate marker for cardiovascular disease. The annualized change in maximum carotid intima–media thickness, the primary end point of the study, did not differ significantly between patients with familial hypercholesterolemia who were treated with atorvastatin alone and those treated with a combination of atorvastatin and torcetrapib. In fact, carotid intima–media thickness of the common carotid artery, a secondary end point of our study, provided evidence of accelerated atherogenesis in the patients who were receiving torcetrapib. It is highly unlikely that

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Monotherapy (N = 427)</th>
<th>Atorvastatin plus Torcetrapib (N = 423)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median (IQR)</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline</td>
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<tr>
<td>Maximum carotid intima–media thickness for each of the 12 carotid-artery sites</td>
<td>1.15±0.31</td>
<td>1.09 (0.93–1.33)</td>
<td>1.13±0.28</td>
</tr>
<tr>
<td>Maximum carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>1.01±0.23</td>
<td>0.98 (0.83–1.17)</td>
<td>0.99±0.22</td>
</tr>
<tr>
<td>Mean carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>0.72±0.15</td>
<td>0.70 (0.60–0.82)</td>
<td>0.71±0.15</td>
</tr>
<tr>
<td>24-Mo follow-up</td>
<td></td>
<td></td>
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<td>Maximum carotid intima–media thickness for each of the 12 carotid-artery sites</td>
<td>1.16±0.33</td>
<td>1.09 (0.94–1.32)</td>
<td>1.14±0.29</td>
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<td>Maximum carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>1.00±0.22</td>
<td>0.97 (0.83–1.13)</td>
<td>1.00±0.21</td>
</tr>
<tr>
<td>Mean carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>0.71±0.14</td>
<td>0.70 (0.61–0.80)</td>
<td>0.72±0.14</td>
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</table>

<table>
<thead>
<tr>
<th>Annualized change from longitudinal model</th>
<th>Slope</th>
<th>SE</th>
<th>Slope</th>
<th>SE</th>
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<tbody>
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<td>0.0028</td>
<td>0.0047</td>
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<td>Maximum carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>−0.0042</td>
<td>0.0025</td>
<td>0.0040</td>
<td>0.0025</td>
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<tr>
<td>Mean carotid intima–media thickness for each of the 4 common carotid-artery sites</td>
<td>−0.0014</td>
<td>0.0013</td>
<td>0.0038</td>
<td>0.0013</td>
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</tbody>
</table>

*Plus–minus values are means ±SD. IQR denotes interquartile range, and SE standard error.
†Number was calculated by the last-observation-carried-forward method.
the unanticipated outcome of this trial can be attributed to the measurement of carotid intima–media thickness itself. This marker has previously been shown to constitute a strong and accurate predictor of the risk of future vascular events in population studies. Furthermore, in evaluations of the efficacy of lipid-modifying medication, antioxidant, estrogen, and antihypertensive drugs, measurements of carotid intima–media thickness were successfully applied and were in line with the outcome of subsequent morbidity and mortality trials.

To account for the observed results, the potential benefit of the observed decrease in LDL cholesterol levels needs to be weighed against the detrimental effect of the rise in systolic blood pressure. The divergent effects of torcetrapib, as compared with atorvastatin alone, on LDL cholesterol (a decrease of 21%) and on systolic blood pressure (an increase of 2.8 mm Hg) are two prominent factors that may have affected carotid intima–media thickness. In a 2-year study of pravastatin, the Regression Growth Evaluation Statin Study (REGRESS), a similar 28% decrease in LDL cholesterol levels was associated with a decrease of 0.05 mm in carotid intima–media thickness. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, the addition of ezetimibe to high-dose simvastatin therapy was designed to reduce LDL cholesterol levels by 18 to 23% and was powered to detect a mean 2-year absolute difference of 0.05 mm in carotid intima–media thickness in 650 patients who were heterozygous for familial hypercholesterolemia. The extrapolation of these findings to our study would suggest that the effect on LDL cholesterol levels would translate into a difference of 0.03 to 0.05 mm in carotid intima–media thickness in favor of the torcetrapib-atorvastatin group.

In contrast, the observed increase in systolic blood pressure can be expected to have an adverse effect on carotid intima–media thickness. In an attempt to account for this effect, we used data from a recent meta-analysis on the relationship between systolic blood pressure and carotid intima–media thickness. That analysis suggests that the effect of the 2.8 mm Hg increase in systolic blood pressure would favor the atorvastatin-only group by 0.014 mm at 2 years. The net opposing effect of the LDL cholesterol level and systolic blood pressure should have left a residual benefit for patients in the torcetrapib–atorvastatin group. The fact that none was observed leaves no possibility of any beneficial effect of the large increase in HDL cholesterol.

In line with the concept that elevation in levels of HDL cholesterol protects against atherosclerosis, small and moderate increases in HDL cholesterol levels, as achieved by the use of nicotinic acid (21%) and gemfibrozil (6%), have previously been reported to yield a significant reduction in the rate of progression of carotid intima–media thickness and in the risk of major cardiovascular events. The absence of an effect of a much greater increase in HDL cholesterol (52%) in our study indicates that torcetrapib either has an adverse vascular effect that negated the changes in lipoprotein levels or that CETP inhibition is not an effective therapeutic strategy. Although our study cannot determine which hypothesis is accurate, there are several possibilities that merit consideration.

With respect to the discrepancy between the remarkable effects of torcetrapib on lipid metabolism and its effects on carotid intima–media thickness, a direct vasculotoxic effect — as shown by a rise in blood pressure — appears to be a possible explanation. The natural ability of HDL to induce vasorelaxation, an effect that is thought to be mediated through scavenger receptor B1, may be adversely affected by torcetrapib.

Another possibility relates to the fact that in-
hition of CETP by torcetrapib actually increases plasma levels of CETP. At a daily dose of 60 mg, torcetrapib continuously increases levels of CETP, a finding that is ascribed to an enhanced affinity of CETP for HDL. This complex formation (CETP–torcetrapib–HDL) is in turn associated with extreme elevations of large HDL particles, as exemplified by the substantial increase in levels of HDL2 cholesterol (157%). In this context, it is worrisome that HDL cholesterol levels were found to increase steadily over the duration of the trial (Fig. 1). It can be hypothesized that HDL cholesterol levels did not affect levels of C-reactive protein.

In contrast, monotherapy with a similar dose of rapib did not affect levels of C-reactive protein. The possibility that HDL may have lost its antiinflammatory potential is illustrated by the observation that torcetrapib did not affect levels of C-reactive protein. In conclusion, the use of torcetrapib in patients with familial hypercholesterolemia did not result in regression of atherosclerosis, as assessed by a combined measure of thickness of the carotid-artery wall, and even caused progression of disease in the common carotid segment. These effects occurred despite an unparalleled increase in the HDL cholesterol level (52%) and a substantial decrease in the LDL cholesterol level (21%).

Supported by Pfizer.

Dr. Kastelein reports receiving consulting fees and lecture fees from Pfizer, AstraZeneca, Merck, and Schering-Plough and grant support from Pfizer and AstraZeneca; Dr. Evans, receiving consulting fees from AstraZeneca and grant support from the National Heart, Lung, and Blood Institute and Pfizer; Dr. Bots, receiving consulting fees from Pfizer, AstraZeneca, Abbott; lecture fees from Pfizer, AstraZeneca, Abbott, and Merck; and grant support from Pfizer; Drs. Revkin, Shear, and Duggan, being employees of Pfizer; Dr. Grobbee, receiving consulting fees and lecture fees from Pfizer, AstraZeneca, Servier, and Organon and grant support from Pfizer, AstraZeneca, Servier, and Organon; and Dr. Bots, receiving consulting and lecture fees and grant support from Pfizer, AstraZeneca, and Servier. No other potential conflict of interest relevant to this article was reported.

We thank Rudy Meijer in Schoorl, the Netherlands, for the design of the image-acquisition protocol, training, and quality control; and T. Roberts, D. Ambrose, A. Chiu, W. Davidson, R. Burnside, A. Caffrey, M. Li, and A. O’Reilly at Pfizer.

APPENDIX


In addition to the authors, the following investigators participated in this study: Tegger Hospital, Parou, Cape Town, South Africa — L. Burgess; Cape Heart Centre University of Cape Town Health Science Faculty, Cape Town, South Africa — A. Marais; Johannes Burgh Hospital, Parktown, Johannesburg, South Africa — F. Raal; General University Hospital, Prague, Czech Republic — R. Ceska; Academisch Medisch Centrum, Amsterdam — M. Trig; Andro Medical Research, Rotterdam, the Netherlands — E. Sijbrands; Clinique des Maladies Lipidiques de Quebec, Place de la Cité, Quebec, QC, Canada — C. Gagne; Vascular Onderzoeker Centrum Hoorn, the Netherlands — D. Bassant; Academisch Ziekenhuis Leiden Afdeiling Inwendige Geneeskunde, Leiden, the Netherlands — M. Huisman; Universiteits Medisch Centrum Utrecht, Utrecht, the Netherlands — F. Visseren; University of Utah, Salt Lake City — P. Hopkins; TuusSildien Ziekenhuis, Waalwijk, the Netherlands — B. Imhol; Universitas Medisc Centrum Sint Radboud, Nijmegen, the Netherlands — A. Stalenhoef; Oulu University Hospital, Oys, Finland — M. Savolainen; Hartford Hospital, Hartford, CT — P. Thompson; Centre de Médecine Génétique Communautaire, Chicoutimi, QC, Canada — D. Gaudet; Clinical Research Institute of Montreal, Montreal — J. Davignon; University of Kuopio, Research Institute of Public Health, Kuopio, Finland — J. Salonen; Universita dei studi di Brescia, Brescia, Italy — E. Agabiti Roselli; Institute for Clinical and Experimental Medicine, Prague, Czech Republic — R. Cifkova; University of Washington, Seattle — R. Knopp; Hopital de la Pitié–Salpetriere, Paris — E. Bruckert; Medisch Centrum Almzaar, Almzaar, the Netherlands — J. Sepers; Oosterschids Ziekenhuis, Goes, the Netherlands — A. Lien; Andremed Noord, Groningen, the Netherlands — J. Jonker; Albert Schweitzer Ziekenhuis, Sliedrecht, the Netherlands — A. Cleophas; Health Sciences Centre, Winnipeg, MB, Canada — D. Myrm; Massachusetts General Hospital, Boston — L. Hemphill, R. Lees; Baylor College of Medicine, Houston — C. Ballantyne; IRCSS Fondazione C. Mondino, Pavia, Italy — A. Cavallini; Reiner de Graaf Gasthuis/Cardio Research, Deft, the Netherlands — A. Wirta- gen; Diakonessenhuis, Ziekenhuis Geneske, Utrecht, the Netherlands — M. Van De Ree; St. Paul’s Hospital, Vancouver, BC, Canada — J. Frohlich; Columbia–Presbyterian Medical Center, New York — H. Ginsberg; University of Minnesota, Minneapolis — D. Duprez; and Hospitale Jeanne d’Arc Centre d’Investigation Clinique, Toul, France — B. Guerci.

REFERENCES


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Omeprazole before Endoscopy in Patients with Gastrointestinal Bleeding


BACKGROUND
A neutral gastric pH is critical for the stability of clots over bleeding arteries. We investigated the effect of preemptive infusion of omeprazole before endoscopy on the need for endoscopic therapy.

METHODS
Consecutive patients admitted with upper gastrointestinal bleeding underwent stabilization and were then randomly assigned to receive either omeprazole or placebo (each as an 80-mg intravenous bolus followed by an 8-mg infusion per hour) before endoscopy the next morning.

RESULTS
Over a 17-month period, 638 patients were enrolled and randomly assigned to omeprazole or placebo (319 in each group). The need for endoscopic treatment was lower in the omeprazole group than in the placebo group (60 of the 314 patients included in the analysis [19.1%] vs. 90 of 317 patients [28.4%], $P=0.007$). There were no significant differences between the omeprazole group and the placebo group in the mean amount of blood transfused (1.54 and 1.88 units, respectively; $P=0.12$) or the number of patients who had recurrent bleeding (11 and 8, $P=0.49$), who underwent emergency surgery (3 and 4, $P=1.00$), or who died within 30 days (8 and 7, $P=0.78$). The hospital stay was less than 3 days in 60.5% of patients in the omeprazole group, as compared with 49.2% in the placebo group ($P=0.005$). On endoscopy, fewer patients in the omeprazole group had actively bleeding ulcers (12 of 187, vs. 28 of 190 in the placebo group; $P=0.01$) and more omeprazole-treated patients had ulcers with clean bases (120 vs. 90, $P=0.001$).

CONCLUSIONS
Infusion of high-dose omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy. (ClinicalTrials.gov number, NCT00164866.)
In patients with bleeding peptic ulcers, we previously showed that infusion of a high-dose proton-pump inhibitor after hemostasis had been achieved during endoscopy reduced recurrent bleeding and improved clinical outcomes. The adjuvant use of high-dose proton-pump inhibitors in endoscopic therapy has also been endorsed in two consensus statements and confirmed in two meta-analyses. Clot formation over arteries is pH dependent; a gastric pH above 6 is thought to be critical for platelet aggregation. When given intravenously and at a high dose, proton-pump inhibitors can be used to maintain a neutral gastric pH. In clinical practice, treatment with proton-pump inhibitors is often initiated before endoscopy in patients presenting with upper gastrointestinal bleeding. However, there is a lack of evidence in the literature to provide support for such a preemptive approach. We hypothesized that early intravenous infusion of a high-dose proton-pump inhibitor before endoscopy would have a therapeutic effect on bleeding ulcers, reduce the need for endoscopic therapy, and result in improved clinical outcomes.

**Methods**

**Study design**

This was a double-blind, placebo-controlled, randomized trial. The study protocol was approved by the ethics committee of the Faculty of Medicine at the Chinese University of Hong Kong. All patients or their legal representatives provided written informed consent for participation in the trial, according to Good Clinical Practice guidelines. There was no pharmaceutical industry support for this study. The authors vouch for the completeness and veracity of the data and data analyses.

**Patients**

Consecutive patients who presented with overt signs of upper gastrointestinal bleeding (i.e., melena or hematemesis with or without hypotension) to the Accident and Emergency Department at the Prince of Wales Hospital in Hong Kong were evaluated by admitting residents for inclusion in the trial. Patients with hypotensive shock (systolic blood pressure ≤90 mm Hg or pulse ≥110 beats per minute) were initially resuscitated and were then considered for entry in the trial if their condition had been stabilized. Patients with continued shock despite initial volume resuscitation (refractory shock) underwent urgent endoscopy and were excluded. We also excluded patients who were younger than 18 years of age, unable to provide written informed consent, or pregnant; those with a known allergy to proton-pump inhibitors; and those who were using aspirin regularly for cardiovascular protection. Long-term aspirin users were enrolled in another randomized study, which evaluated the effect of early reintroduction of aspirin on the risk of recurrent ulcer bleeding.

For patients who had bleeding ulcers associated with ingestion of nonsteroidal antiinflammatory drugs, the drugs were discontinued. Patients who had life-threatening bleeding and were using warfarin or had bleeding from an overdose of warfarin were given vitamin K or fresh-frozen plasma. Patients for whom anticoagulation was considered necessary (e.g., patients with prosthetic heart valves or pulmonary embolism within 6 months) underwent heparin therapy until the bleeding was stabilized.

**Study procedures**

Patients were randomly assigned to receive an intravenous infusion of omeprazole (Losec, AstraZeneca) or placebo, each given as an 80-mg intravenous bolus injection followed by continuous infusion of 8 mg per hour until endoscopic examination the next morning. Identical-appearing vials of omeprazole and placebo were prepared at the School of Pharmacy under aseptic conditions, according to the International Good Manufacturing Practice Guidelines for Pharmaceuticals. The vials were sealed in packages and numbered according to a computer-generated list of random numbers in blocks of 20, without stratification. The consecutively numbered, sealed packages were delivered to the admission ward. After obtaining written informed consent for a given patient, the admitting resident opened the lowest-numbered package. Use of omeprazole or placebo was started at admission and was stopped at the endoscopy center just before endoscopy was begun. Urgent endoscopy was performed (without stopping the omeprazole or placebo) in patients with signs of ongoing bleeding (i.e., fresh hematemesis or hematochezia, hypotensive shock, or both) as judged by ward residents or attending physicians. All vials were returned to our research office at the end of the infusion period to assess whether the drug had been delivered correctly and completely. All investigators were unaware of the group assignments.

At endoscopy, gastroduodenal ulcers with spurt- ing hemorrhage, oozing hemorrhage, or nonbleed-
ing visible vessels (defined as protuberant discolorations) were injected with epinephrine (dilution, 1:10,000). Aliquots of epinephrine (0.5 to 1 ml) were injected around the bleeding vessel with the use of a 23-gauge sclerotherapy needle until bleeding had completely ceased. Coaptive thermocoagulation was then applied to vessels with the use of a 3.2-mm heater probe (model CD-10Z, Olympus).

**Figure 1.** Enrollment and Randomization of Study Patients.

The 350 patients excluded because of chronic aspirin use were enrolled in a parallel study in which regular aspirin users were randomly assigned to receive aspirin or placebo after endoscopic hemostasis of their bleeding peptic ulcers had been achieved and after adjunctive use of a high-dose proton-pump inhibitor (PPI) had been initiated intravenously.9
Hemostasis was considered to have been established if bleeding had stopped and if formerly bleeding vessels were flattened or cavitated. Clots covering ulcer craters were elevated by means of irrigation through a heater probe for up to 5 minutes or “cheese-wiring” with a mini-snare, and underlying vessels, if present, were treated. Preinjection with diluted epinephrine at the pedicle of the clot was permitted. Antral-biopsy specimens were obtained and subjected to a rapid urease test (CLO test, Delta West) and histologic examination to determine whether Helicobacter pylori infection was present. Bleeding esophageal and gastric varices were treated with the use of band ligation and injection of cyanoacrylate (a tissue adhesive), respectively, in addition to the use of vasoactive drugs and intravenous antibiotics.

At the end of each therapeutic procedure, the

| Table 1. Characteristics of the 631 Patients Included in Analyses.† |
|-------------------|-------------------|-------------------|-------------------|
| Characteristic                             | Omeprazole (N = 314) | Placebo (N = 317) | P Value |
| Age — yr                                   | 61.7 ± 17.9         | 62.3 ± 17.5       | 0.67    |
| Male sex — no. (%)                         | 208 (66.2)          | 201 (63.4)        | 0.46    |
| Hemoglobin — g/dl                          | 10.3 ± 2.9          | 10.4 ± 7.6        | 0.73    |
| Hematocrit — %                             | 0.30 ± 0.08         | 0.33 ± 0.59       | 0.40    |
| No. of units of blood transfused before endoscopy |                     |                   |         |
| Mean ±SD                                   | 0.76 ± 1.11         | 0.85 ± 1.21       | 0.26    |
| Median (range)                             | 0 (0–4)             | 0 (0–6)           | 0.37    |
| Systolic blood pressure — mm Hg            | 116.2 ± 20.4        | 117.3 ± 21.9      | 0.56    |
| Systolic blood pressure < 90 mm Hg — no. of patients (%) | 30 (9.6)            | 28 (8.8)          | 0.78    |
| ASA grade — no. of patients (%)             |                     |                   |         |
| I                                           | 121 (38.5)          | 117 (36.9)        | 0.78    |
| II                                          | 126 (40.1)          | 125 (39.4)        |         |
| III or IV                                   | 67 (21.3)           | 75 (23.7)         |         |
| Coexisting illness — no. of patients        |                     |                   |         |
| Cirrhosis                                   | 17                  | 19                | 0.86    |
| Cancer                                      | 32                  | 23                | 0.21    |
| Cardiovascular disease                      | 18                  | 25                | 0.34    |
| Chronic renal failure                       | 2                   | 3                 | 1.00    |
| Bleeding during hospitalization — no. of patients (%) | 12 (3.8)           | 9 (2.8)           | 0.49    |
| Risk factors for bleeding peptic ulcer — no. of patients (%) |                     |                   |         |
| Use of NSAID other than aspirin             | 70 (22.3)           | 74 (23.3)         | 0.75    |
| Use of warfarin                             | 6 (1.9)             | 12 (3.8)          | 0.16    |
| Use of aspirin                              | 5 (1.6)             | 8 (2.5)‡          | 0.41    |
| Previous ulcer disease — no. of patients (%) | 80 (25.5)          | 80 (25.2)         | 1.00    |
| Previous bleeding — no. of patients (%)     | 68 (21.7)           | 66 (20.8)         | 0.85    |
| Use of PPI or histamine-receptor antagonist within past 4 wk — no. of patients (%) | 38 (12.1)           | 40 (12.6)         | 0.90    |
| Peptic ulcer as source of bleeding — no. of patients (%) | 187 (59.6)          | 190 (59.9)        | 0.94    |
| Duodenal ulcer                              | 88                  | 102               |         |
| Gastric ulcer                               | 75                  | 67                |         |
| Both                                        | 14                  | 13                |         |
| Anastomotic ulcers                          | 10                  | 8                 |         |
| Esophageal or gastric varices — no. of patients (%) | 10 (3.2)           | 14 (4.4)          | 0.53    |
endoscopist was required to rate the difficulty of the procedure on a 10-cm visual-analogue scale (with 0 cm indicating an easy procedure, 10 cm indicating a difficult procedure, and no gradations in between). Patients who did not require endoscopic therapy were returned to the general medical ward. Those who underwent endoscopic therapy were subsequently transferred to a medical gastroenterology ward for monitoring.

Omeprazole (8 mg per hour) was infused for 72 hours after endoscopy in patients who required ulcer hemostasis. Bleeding was considered to have recurred if any of the following occurred: vomiting of fresh blood, hypotensive shock (defined as a systolic blood pressure ≤90 mm Hg or a pulse ≥110 beats per minute) with melena after stabilization, or a decrease in the hemoglobin level of more than 2 g per deciliter and a decrease in the hematocrit of more than 6% within 24 hours after a transfusion, resulting in a hemoglobin level of 10 g per deciliter or less. Patients who were judged to have recurrent bleeding underwent urgent endoscopy by endoscopists on duty. Recurrent bleeding was confirmed if the ulcer was actively bleeding (spurting or oozing hemorrhage) or if there was fresh blood in the stomach and a vessel at the ulcer base. Clots overlying ulcers were lifted, and the base of the ulcer was examined. Endoscopic therapy was repeated on the bleeding artery. Surgical intervention was deemed to be warranted if the bleeding could not be controlled by endoscopic methods or if

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Omeprazole (N=314)</th>
<th>Placebo (N=317)</th>
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<td>95/178 (53.4)</td>
<td>109/182 (59.8)</td>
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<td>238</td>
<td>243</td>
<td>0.43</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>68</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Duration of infusion before endoscopy — hr</td>
<td>14.7±6.3</td>
<td>15.2±6.2</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. NSAID denotes nonsteroidal antiinflammatory drug, and PPI proton-pump inhibitor.
† The American Society of Anesthesiologists (ASA) grades are assigned as follows: I for a healthy patient; II for a patient with mild systemic disease, such as mild diabetes or hypertension or slightly limiting organic heart disease; III for a patient with severe systemic disease that is not incapacitating; IV for a patient with incapacitating systemic disease that is life threatening, such as a patient with marked cardiac insufficiency, persistent angina, and advanced pulmonary, hepatic, renal, or endocrine insufficiency; and V for a patient who is not expected to survive for more than 24 hours, with or without surgery.
‡ One of the eight patients was using both aspirin (80 mg) and clopidogrel (75 mg) daily.
§ Dieulafoy’s lesion is a rare cause of acute upper gastrointestinal bleeding. It is usually found within 6 cm of the gastroesophageal junction, high in the body of the stomach or in its fundus. Histopathological examination of a resected Dieulafoy’s lesion shows an unusually large and tortuous artery located just underneath the muscularis mucosae.
¶ Infection with H. pylori was diagnosed on the basis of a positive rapid urease test (CLO test, Delta West) or detection of the bacteria during histologic examination.
there was a second recurrence of bleeding.

After the 72-hour infusion of omeprazole, patients were given 40 mg of omeprazole orally per day for 8 weeks. Patients who had a positive rapid urease test for *H. pylori* received a 1-week course of 20 mg of omeprazole twice daily, 500 mg of clarithromycin (Klacid, Abbott) twice daily, and 1 g of amoxicillin (Amoxil, SmithKline Beecham) twice daily. These patients then received the standard dose of 40 mg of omeprazole per day for the remaining 7 weeks. We followed patients until day 30 after randomization. Research nurses contacted patients or their families. Records of hospital readmissions, clinic follow-up, and death were obtained and verified through a regional computerized hospital-record system. Eradication of *H. pylori* was confirmed with the use of a rapid urease test and histologic analysis during follow-up endoscopy at 8 weeks.

**END POINTS**

Our primary end point was the need for endoscopic therapy at the first endoscopic examination. Secondary end points included signs of bleeding, need for urgent endoscopy, duration of hospital stay, need for transfusion, need for emergency surgery to achieve hemostasis, and rates of recurrent bleeding and death from any cause within 30 days after randomization.

**STATISTICAL ANALYSIS**

We calculated that 174 patients with bleeding peptic ulcers would have to be enrolled in each group for the study to have a statistical power of 90% to detect an absolute reduction of 15% (from 30% to 15%) in the rate of endoscopic therapy with the use of preemptive infusion of high-dose omeprazole for bleeding peptic ulcers on scheduled endoscopy, with a two-sided alpha level of 0.05. Assuming that 60% of our patients presenting with upper gastrointestinal bleeding had bleeding from peptic ulcers, we then calculated that we would need to enroll a total of 290 patients in each group. In addition, we assumed that we would not be able to evaluate 10% of our enrolled patients. A minimum of 319 patients would therefore be needed in each group. One interim analysis was planned, the results of which have been published previously. The level of significance of the observed difference in the primary end point did not fulfill the Peto–Haybittle criterion (i.e., P<0.001) for early termination.

All analyses were based on the intention-to-treat principle. Fisher’s exact test was used to analyze the primary end point, the need for endoscopic therapy, in the two groups. We calculated the effect of omeprazole as compared with that of placebo by using relative risks and the corresponding 95% confidence intervals (CIs). The Kaplan–Meier method with the log-rank test was used to compare differences in the rates of recurrent bleeding and death within 30 days after randomization. All tests of significance were two-tailed, and a P value of 0.05 was considered to indicate statistical significance.

**RESULTS**

During a 17-month period between February 2004 and July 2005, a total of 638 patients were enrolled; 319 were randomly assigned to receive omeprazole and 319 to receive placebo (Fig. 1). Seven patients (five in the omeprazole group and two in the placebo group) were excluded from analysis: three withdrew before omeprazole or placebo was administered and four had received a misdiagnosis of upper gastrointestinal bleeding (two actually had small-bowel obstruction, one had undergone a total gastrectomy, and one had cholangitis). Two patients in the omeprazole group did not undergo endoscopy (one refused and one became moribund). Baseline demographic and clinical characteristics were similar in the two groups (Table 1).

Thirteen patients (five in the omeprazole group and eight in the placebo group) presented with aspirin-related upper gastrointestinal bleeding. They were found to have no indications for the long-term use of aspirin and were therefore not eligible for the parallel study of long-term aspirin users; instead, they were enrolled in our study. The source of bleeding was peptic ulcer in 187 of 314 patients (59.6%) in the omeprazole group and 190 of 317 patients (59.9%) in the placebo group. The mean (±SD) duration of infusion before endoscopy was 14.7±6.3 hours in the omeprazole group and 15.2±6.2 hours in the placebo group.

Of the 314 patients in the omeprazole group, 60 (19.1%) required endoscopic treatment, as compared with 90 of the 317 patients (28.4%) in the placebo group (relative risk for the omeprazole group, 0.67; 95% CI, 0.51 to 0.90; P=0.007). Among patients with peptic-ulcer bleeding, 42 of 187 pa-
Table 2. Outcomes for the 631 Patients Included in the Analyses.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Omeprazole (N=314)</th>
<th>Placebo (N=317)</th>
<th>P Value</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic therapy — no. of patients (%)</td>
<td>60 (19.1)</td>
<td>90 (28.4)</td>
<td>0.007</td>
<td>0.67 (0.51–0.90)</td>
</tr>
<tr>
<td>Endoscopic therapy for bleeding peptic ulcers — no. of patients/total no. with peptic ulcers (%)</td>
<td>42/187 (22.5)</td>
<td>70/190 (36.8)</td>
<td>0.002</td>
<td>0.61 (0.44–0.84)</td>
</tr>
<tr>
<td>Volume of injected diluted epinephrine — ml</td>
<td>9.2±6.0</td>
<td>10.5±7.0</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>No. of pulses of heater probe — median (range)</td>
<td>5 (2–16)</td>
<td>6 (2–18)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Endoscopic therapy for other sources of bleeding — no. of patients (%)</td>
<td>18 (5.7)</td>
<td>20 (6.3)</td>
<td>0.87</td>
<td>0.90 (0.49–1.68)</td>
</tr>
<tr>
<td>Endoscopic signs of bleeding in peptic ulcers — no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active bleeding</td>
<td>12</td>
<td>28</td>
<td>0.01</td>
<td>0.44 (0.23–0.83)</td>
</tr>
<tr>
<td>Nonbleeding visible vessel</td>
<td>23</td>
<td>31</td>
<td>0.30</td>
<td>0.75 (0.45–1.24)</td>
</tr>
<tr>
<td>Clot with underlying vessel</td>
<td>7</td>
<td>11</td>
<td>0.47</td>
<td>0.65 (0.26–1.63)</td>
</tr>
<tr>
<td>Flat, pigmented spot</td>
<td>25</td>
<td>30</td>
<td>0.56</td>
<td>0.85 (0.52–1.38)</td>
</tr>
<tr>
<td>Clean base</td>
<td>120</td>
<td>90</td>
<td>0.001</td>
<td>1.35 (1.13–1.63)</td>
</tr>
<tr>
<td>Urgent endoscopy — no. of patients</td>
<td>7</td>
<td>6</td>
<td>0.79</td>
<td>1.18 (0.40–3.44)</td>
</tr>
<tr>
<td>For bleeding peptic ulcers</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For other causes of bleeding</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1402</td>
<td>1570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>4.5±5.3</td>
<td>4.9±5.1</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1–43)</td>
<td>3 (1–54)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Hospital stay &lt;3 days — no. of patients (%)</td>
<td>190 (60.5)</td>
<td>156 (49.2)</td>
<td>0.005</td>
<td>1.23 (1.07–1.42)</td>
</tr>
<tr>
<td>Death within 30 days — no. of patients (%)</td>
<td>8 (2.5)</td>
<td>7 (2.2)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Difficulty with endoscopic therapy†</td>
<td>4.2±2.6</td>
<td>4.8±2.7</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Units of blood transfused</td>
<td>1.54±2.41</td>
<td>1.88±3.44</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Emergency surgery — no. of patients/total no. with peptic ulcers (%)</td>
<td>3/187 (1.6)</td>
<td>4/190 (2.1)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Partial gastrectomy — no. of patients</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagotomy and pyloroplasty</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer excision</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omental patch repair (for a perforated duodenal ulcer)</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding within 30 days — no. of patients (%)</td>
<td>11 (3.5)</td>
<td>8 (2.5)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Bleeding peptic ulcers</td>
<td>8</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding Mallory–Weiss tear</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. CI denotes confidence interval.
† Difficulty was reported on a 10-cm visual-analogue scale, with 0 cm indicating an easy procedure and 10 cm indicating a difficult procedure, with no gradations in between.
Patients (22.5%) in the omeprazole group and 70 of 190 patients (36.8%) in the placebo group required endoscopic treatment (relative risk, 0.61; 95% CI, 0.44 to 0.84; P = 0.002) (Table 2). The mean volume of injected epinephrine was lower in the omeprazole group than in the placebo group (9.2 ± 6.0 ml vs. 10.5 ± 7.0 ml, P = 0.31), as was the median number of pulses of heater probe used (5 [range, 2 to 16] vs. 6 [2 to 18], P = 0.01).

Among patients with peptic-ulcer bleeding observed during the first endoscopic examination, actively bleeding peptic ulcers were seen less frequently in patients given omeprazole before endoscopy than in those given placebo (in 12 of 187 [6.4%] vs. 28 of 190 [14.7%], P = 0.01) (Fig. 2). In addition, more ulcers with clean bases were seen in the omeprazole group than in the placebo group (in 120 of 187 [64.2%] vs. 90 of 190 [47.4%], P = 0.001). The numbers of nonbleeding visible vessels, clots, and flat, pigmented spots did not differ significantly between the two groups.

Urgent endoscopy was required for seven patients in the omeprazole group and six patients in the placebo group (P = 0.79). Episodes of hypotensive shock (defined as systolic blood pressure ≤ 90 mm Hg or a pulse ≥ 110 beats per minute) occurred during the infusion period in 18 patients in the omeprazole group and 24 patients in the placebo group (P = 0.35). The mean number of units of blood products transfused was 1.54 ± 2.41 in the omeprazole group and 1.88 ± 3.44 in the placebo group (P = 0.12). Three of 187 patients (1.6%) in the omeprazole group and 4 of 190 patients (2.1%) in the placebo group underwent emergency surgery owing to failure to achieve hemostasis during endoscopy. Recurrent bleeding occurred within 30 days after endoscopic therapy in 11 patients (3.5%) in the omeprazole group and 8 patients (2.5%) in the placebo group (P = 0.49 by the log-rank test) (Fig. 3). The hospital stay was significantly shorter in the omeprazole group (median, 3 days [range, 1 to 43] vs. 3 days [1 to 54], P = 0.003). The hospital stay was less than 3 days for 190 patients (60.5%) in the omeprazole group and 156 patients (49.2%) in the placebo group (P = 0.005).

Eight patients (2.5%) in the omeprazole group and seven patients (2.2%) in the placebo group died within 30 days after randomization (P = 0.78 by the log-rank test) (Table 3). Causes of death in the omeprazole group were disseminated cancer (four patients), small-bowel infarction (one patient), peritonitis (one patient), variceal bleeding (one patient), and myocardial infarction (one patient). Causes of death in the placebo group were pancreatic cancer (two patients), bleeding stomach cancer (one patient), colon cancer (one patient),
subarachnoid hemorrhage (one patient), variceal hemorrhage and hepatic failure (one patient), and nosocomial pneumonia (one patient). None of the serious adverse events (Table 3) were judged by investigators to be related to omeprazole or placebo.

Discussion

Our findings reaffirm that optimal acid suppression facilitates clot formation over arteries in bleeding peptic ulcers. On endoscopy, fewer cases of actively bleeding peptic ulcers were seen among patients who had received omeprazole than among those who had received placebo. Early administration of high-dose omeprazole reduced the need for endoscopic therapy. In addition, omeprazole appears to accelerate the resolution of signs of bleeding. More patients in the omeprazole group than in the placebo group had ulcers with clean bases. Early administration of omeprazole therefore permitted more patients to be discharged early. Among our patients awaiting endoscopy, omeprazole stabilized clots, prevented recurrent bleeding, and initiated healing. Because patients in both groups received an infusion of high-dose omeprazole after hemostasis had been achieved, the rates of recurrent bleeding were low. The rate was marginally higher in the omeprazole group. No significant differences were detected between the two groups in any clinical outcomes.

Daneshmend et al. performed a multicenter clinical trial to examine the effect of acid suppression before endoscopy. Bolus injections of omeprazole or placebo were used during the first 24 hours, followed by an oral regimen. Signs of bleeding were found in 33% of patients receiving omeprazole, as compared with 45% of patients given placebo — a finding that was similar to ours. The times to endoscopy, need for therapy, and specific signs of bleeding were not reported.

In a placebo-controlled clinical trial that did not involve endoscopic therapy, Khuroo et al. found that recurrent bleeding was less frequent in patients with nonbleeding visible vessels and clots who were given oral omeprazole than in those given placebo. This finding provides support for the notion that acid suppression confers clot stability among patients with ulcers. However, the same omeprazole treatment did not reduce the rate
of recurrent bleeding among patients with ulcers that were actively bleeding on endoscopy.

Several factors limit the generalizability of our findings. First, we excluded long-term aspirin users who had coexisting cardiovascular conditions. Another ongoing clinical trial in our hospital focused on this subgroup of patients, preventing their inclusion into our study. The effect of high-dose omeprazole on clot stability in patients taking aspirin is unknown. Patients enrolled in our study may therefore have been at low risk. Second, our findings may not be applicable to geographic areas with a higher prevalence of variceal bleeding than that in Hong Kong. In Hong Kong, the source of upper gastrointestinal bleeding is peptic ulcer in approximately 60% of patients.

In patients with upper gastrointestinal bleeding, early endoscopy (usually defined as endoscopy performed within 24 hours after admission) should be the standard of care in most hospitals. In selected high-risk patients, early endoscopy involving therapy stops bleeding and potentially saves lives. Early endoscopy also permits low-risk patients to be discharged early from the hospital. We do not propose using high-dose proton-pump inhibitors as a replacement for early endoscopy. In patients awaiting endoscopy, however, we recommend the preemptive use of high-dose intravenous omeprazole. Although we did not perform a cost analysis, early administration of high-dose omeprazole may prove to be a cost-saving approach owing to reduced use of hospital resources.

Supported by the Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong, China.

Dr. Lau reports receiving consulting fees and lecture fees from AstraZeneca; Dr. Chan, consulting fees from Pfizer; lecture fees from Takeda and TAP Pharmaceutical Products, and grant support from Pfizer; and Dr. Sung, lecture fees from AstraZeneca and GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

REFERENCES

Targeted Therapy for Inherited GPI Deficiency

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Drs. Almeida and Murakami contributed equally to this article.


SUMMARY

Disrupted binding of the transcription factor Sp1 to the mutated promoter region of the mannosyl transferase–encoding gene PIGM causes inherited glycosylphosphatidylinositol (GPI) deficiency characterized by splanchnic vein thrombosis and epilepsy. We show that this results in histone hypoacetylation at the promoter of PIGM. The histone deacetylase inhibitor butyrate increases PIGM transcription and surface GPI expression in vitro as well as in vivo through enhanced histone acetylation in an Sp1-dependent manner. More important, the drug caused complete cessation of intractable seizures in a child with inherited GPI deficiency.

LINKAGE TO GLYCOSYLPHOSPHATIDYLINOSITOL (GPI) IS A MODE OF CELL-SURFACE expression used by proteins of diverse functions. Acquired GPI deficiency, as seen in the clonal disorder paroxysmal nocturnal hemoglobinuria, is characterized by hemolytic anemia, thrombosis, and bone marrow failure. In paroxysmal nocturnal hemoglobinuria, deficiency of GPI-linked proteins is caused by somatic mutations in the X-linked gene PIGA, resulting in a block in the addition of glucosamine to phosphatidylinositol.

We recently described a new form of inherited GPI deficiency presenting in infancy, characterized by splanchnic vein thrombosis and seizures and inherited as an autosomal recessive trait. As compared with paroxysmal nocturnal hemoglobinuria, inherited GPI deficiency does not result in clinically significant hemolysis and bone marrow failure. In the families described so far, partial yet severe GPI deficiency is caused by the blocked addition of the first mannose residue onto the GPI intermediate phosphatidylinositol–glucosamine, a step catalyzed by the α1,4-mannosyltransferase PIGM. The genetic defect in inherited GPI deficiency is a −270C→G mutation in the core promoter of PIGM, which disrupts binding of the transcription factor Sp1 to its cognate motif, resulting in markedly reduced transcription.

Sp1 influences transcription through heterotypic interactions with the basal transcriptional machinery and with other transcription factors and by recruiting histone acetyltransferases and histone deacetylases to the promoter. Histone deacetylase inhibitors such as sodium butyrate enhance transcription and hold promise as therapeutic agents for a variety of diseases, including cancer. For a small number of genes, the hyperacetylation effect of sodium butyrate requires the presence of Sp1-binding elements or a conserved sequence to which an as-yet-unknown transcription factor binds; these promoter elements are also referred to as butyrate response elements. In Sp1-dependent genes containing butyrate response elements, sodium butyrate
may modulate transcription through covalent modification of Sp1 as well as through histone hyperacetylation.7,9

We investigated whether the PIGM promoter contained butyrate response elements and whether modification of acetylation mediated by sodium butyrate could result in enhanced transcription of PIGM, even in the presence of the mutated Sp1-binding motif associated with inherited GPI deficiency.

METHODS

PATIENT AND STUDY DESIGN

The patient was seen at King's College Hospital and Hammersmith Hospital in London. The study was approved by the respective local research ethics committees, and oral informed consent was provided in accordance with the provisions of the Declaration of Helsinki.

CELL LINES AND ANALYSES

The generation of Epstein–Barr virus (EBV)–transformed lymphoblastoid cell lines was described previously.10 For details regarding flow cytometry, real-time polymerase-chain-reaction analysis, reporter assays, and statistical analysis, see the Supplementary Appendix, available with the full text of this article at www.nejm.org. Chromatin immunoprecipitation assays (Upstate Biotechnology) were performed according to the manufacturer’s instructions except for the following modifications: immunoprecipitation was performed with anti-acetylated histone 4 (Upstate Biotechnology) or rabbit IgG (Santa Cruz). After DNA-protein cross-linking reversal and proteinase K digestion, DNA was isolated with the use of a MiniElute PCR purification kit (Qiagen). Primer sequences are available from the authors on request.

RESULTS

CLINICAL REPORT

In 1995, a 2-year-old girl (now 14 years of age) presented with hepatic vein thrombosis and the Budd–Chiari syndrome (Table 1 of the Supplementary Appendix). After one episode of hepatic decompensation owing to variceal bleeding at the age of 5 and two shunt procedures at the age of 7, portal hypertension eventually became well con-

Figure 1 (facing page). Effect of Butyrate In Vitro.

Panel A shows histone acetylation at the PIGM locus. Assessment of the acetylation status of histone 4 was performed with the use of chromatin immunoprecipitation assays. There was no evidence of acetylation at the CD3ε locus in lymphoblastoid cell lines from either the patient or her mother, and this finding did not change in the presence of sodium butyrate. Acetylation was detectable at the locus of GAPDH in both cell lines, and PIGM locus acetylation was present in the cell line of the mother but not of the patient. On exposure to sodium butyrate, acetylation was restored in the patient’s cell line. Results of three independent experiments were similar and are represented as follows: lane 1, immunoprecipitation with IgG monoclonal antibody control; lane 2, immunoprecipitation with antiacetylated histone 4 monoclonal antibody; and lane 3, input nuclear extract. Panel B shows the effects of sodium butyrate (B) and plicamycin (P) on the reporter activity of the firefly luciferase reporter plasmid (pGL3) with wild-type and mutant PIGM promoter. The reporter assays were carried out in HeLa cells, and luciferase activity was measured 48 hours after transfection. The wild-type construct was considered to have 100% activity. Activity of the mutant construct was reduced to 45% (95% CI, 27 to 76). When incubated with 3 mM of sodium butyrate, the reporter protein activity of both wild-type and mutant constructs increased by a factor of 3.1 and 3.5, respectively (95% CI, 1.3 to 7.7 and 2.2 to 5.8, respectively). In the presence of plicamycin, luciferase activity was almost completely absent with both wild-type and mutant constructs, whereas activity of renilla luciferase reporter plasmid (pRL-CMV) was not affected. In the presence of butyrate and plicamycin, promoter activity was similarly reduced for both the wild-type construct (by 82%; 95% CI, 72 to 88) and mutant construct (by 88%; 95% CI, 87 to 90) below butyrate-induced and baseline levels; however, residual activities of 55% and 18%, respectively, were still observed. The columns labeled as empty refer to pGL3 without the PIGM promoter sequences. The means (±SE) of four independent experiments are shown. Panel C shows PIGM RNA levels, as determined by real-time polymerase chain reaction, in affected lymphoblastoid cell lines before and after sodium butyrate treatment. A normal cell line, homozygous for wild-type sequence, and one derived from the mother, heterozygous for the −270C→G mutation, were used as controls. PIGM expression levels in the normal cell line were considered to be 100%. In comparison, PIGM RNA levels in the maternal cell line were 43% of normal (95% CI, 29 to 63), and they were less than 1% of normal in the patient’s cell line before butyrate treatment. After 72 hours of incubation with 3 mM of sodium butyrate, PIGM RNA levels in the patient’s cell line increased by a factor of 407 (95% CI, 257 to 644). The means (±SE) of four independent experiments are shown. Panel D shows the correction of the GPI-negative phenotype in the patient’s cell line after exposure to sodium butyrate. GPI expression, as determined by fluorescent inactivated eosinyl (FLAER) staining and flow cytometry, was completely restored in the patient’s cell line after incubation with 3 mM of sodium butyrate for 72 hours. M1 indicates positive events as determined by the isotypic control set at 1%.
trolled with conservative therapy (spironolactone, propranolol, and oral anticoagulants).

Absence seizures developed at the age of 4 years and were initially well controlled with sodium valproate; lamotrigine was added when the patient was 9 years old after an episode of status epilepticus, with good control of seizures. When she was first seen in the United Kingdom at the age of 9 years, tests for thrombophilia and the results of metabolic screening were normal; the diagnosis of inherited GPI deficiency was made by flow-cytometric analysis of GPI expression on blood cells. During the next 5 years, the frequency of seizures increased progressively despite increases in anticonvulsant therapy. Sodium valproate was stopped and levetiracetam started at the age of 12 years; a year later, topiramate was added. When the patient was seen in the United Kingdom again at the age of 14 years, she was having multiple absence seizures and approximately five tonic–clonic seizures per day; antiepileptic treatment consisted of lamotrigine, levetiracetam, topiramate, and clonazepam (Table 1 of the Supplementary Appendix).

On examination, the patient was wheelchair-bound with global hypotonia, drooling, and extreme drowsiness. She was poorly responsive and
unable to feed herself, symptoms that may have reflected toxic effects of the antiepileptic therapy as well as the disease itself. Central nervous system imaging, including magnetic resonance imaging and magnetic resonance angiography and venography, showed no structural abnormalities or evidence of thrombosis. Findings on electroencephalography performed while the patient was having multiple absence episodes were grossly abnormal, with frequent multifocal and generalized epileptiform discharges and a massive photoconvulsive response, and were consistent with an electrographic diagnosis of nonconvulsive status epilepticus.

**EFFECT OF SODIUM BUTYRATE IN VITRO**

Since Sp1 could be important for histone acetylation,

$^{9,11}$ we studied the effect of the $-270C\to G$ mutation on the acetylation status of histone 4 in the promoter region of *PIGM*, using chromatin immunoprecipitation assays. As expected, there was no evidence of histone acetylation in the promoter of the T-cell–specific gene *CD3e* in lymphoblastoid B-cell lines from either the patient or her mother (Fig. 1A). Consistent with the function of a housekeeping gene, histone 4 at the promoter of *GAPDH* was fully acetylated in both cell lines. Similarly, acetylation at *PIGM*, itself a housekeeping gene, was also readily detected in the maternal lymphoblastoid cell line. However, in the patient’s cell line, there was no evidence of histone acetylation at the *PIGM* promoter, suggesting that the $-270$ Sp1-binding motif is crucial for histone acetylation. Histone 4 acetylation was fully restored on exposure of the patient’s lymphoblastoid cell line to sodium butyrate, which suggested the presence of promoter sequences that on inhibition of histone deacetylases could substitute for the disrupted $-270$ motif in promoting histone hyperacetylation.

To test whether inhibition of histone deacetylases could affect *PIGM* transcription through Sp1, we tested the effect of sodium butyrate in luciferase reporter assays, using wild-type or mutant *PIGM* promoter constructs. As shown previously, the $-270C\to G$ mutation resulted in a 55% reduction in *PIGM* promoter activity (Fig. 1B). In the presence of sodium butyrate, transcriptional activity increased by a factor of approximately 3 with both constructs. In the presence of plicamycin (formerly called mithramycin), an agent that blocks Sp1 binding to DNA,$^{12,13}$ transcriptional activity was almost entirely abolished for both constructs, suggesting that Sp1 binding is critical for efficient transcription of *PIGM*. Plicamycin similarly reduced but did not completely abolish sodium butyrate–enhanced transcriptional activity: 55% and 18% residual activity was observed for the wild-type and mutant constructs, respectively.

The increased transcriptional activity of the *PIGM* promoter in the presence of sodium butyrate was accompanied by an increase by a factor of 400 in *PIGM* messenger RNA (mRNA) levels in the patient’s cell line (Fig. 1C). At the same time, expression of surface GPI, as assessed by fluorescently activated aerolysin (FLAER) staining, was completely restored (Fig. 1D). Taken together, these findings suggested that sodium butyrate–mediated transcriptional activation could take place even in the presence of the mutated Sp1 motif, causing inherited GPI deficiency. In addition to being histone hyperacetylation–dependent, this effect is also Sp1 binding–dependent and, to a lesser extent, Sp1-independent.
**A**

**Before Butyrate**

- **Erythrocytes**
  - No. of Cells
  - CD59
  - FLAER

- **Granulocytes**
  - No. of Cells
  - CD59
  - CD24

**After Butyrate**

- **Erythrocytes**
  - No. of Cells
  - CD59
  - FLAER

- **Granulocytes**
  - No. of Cells
  - CD59
  - CD24

**B**

- Sodium phenylbutyrate
  - 20 mg/kg
  - 50 mg/kg

- Days of Therapy
  - Positivity [%]
  - CD59
  - CD24
  - FLAER

**C**

- Relative PGM RNA Levels
  - Normal
  - Mother
  - Patient before Butyrate
  - Patient after Butyrate
EFFECT OF SODIUM BUTYRATE IN VIVO

In view of the intractable seizures experienced by the patient and guided by the effectiveness of sodium butyrate in restoring PIGM transcription and GPI expression in vitro by the mutant as well as the wild-type promoter, we started clinical therapy with sodium phenylbutyrate at a dose of 20 mg per kilogram of body weight three times a day. At the same time, levetiracetam, clobazam, and lamotrigine were withdrawn and sodium valproate added.

The in vivo effect of sodium phenylbutyrate on PIGM RNA levels and on surface GPI was assessed prospectively in peripheral-blood cells. A progressive increase in the proportions of granulocytes staining positive for FLAER and two GPI-linked proteins was observed, as compared with levels before the administration of sodium phenylbutyrate. Assessment of the effect of this treatment on PIGM transcription showed that 3 months after therapy began, PIGM mRNA levels in primary mononuclear blood cells increased by a factor of nearly 70 from baseline (from 0.5 to 33.0%) (Fig. 2C). Thus, sodium phenylbutyrate increased PIGM transcription and cell-surface GPI expression in vivo as well as in vitro.

An equally dramatic clinical effect was observed (Table 1 of the Supplementary Appendix). The general condition of the patient improved, and she could perform activities that she had been unable to perform for 2 to 3 years — namely, to walk, interact, and feed herself. More important, within 2 weeks after the treatment modification began, she became entirely seizure-free and remained so for 2 to 3 years — namely, to walk, interact, and feed herself. More important, when the dose of sodium phenylbutyrate was increased to 30 mg per kilogram three times a day after 8 weeks.

DISCUSSION

We show here that binding of Sp1 to its core promoter motif is crucial for control of the acetylation status and transcriptional activity at the PIGM promoter, findings with important therapeutic implications for patients with inherited GPI deficiency. As shown in Figure 1A, the −270 motif is required for maintenance of histone acetylation in the PIGM promoter. Its disruption by the mutation responsible for inherited GPI deficiency results in significant reduction in acetylation, PIGM transcription, and synthesis and cell-surface expression of GPI. These findings are consistent with the previously described function of Sp1 in regulating transcription through recruitment to the promoter of histone acetyltransferases,14,15 histone deacetylases,7,15 or both and its function through histone acetylation.

Despite disruption of Sp1 binding to the −270 motif, sodium butyrate increased histone acetylation and transcriptional activity of the mutant PIGM promoter, thereby restoring surface GPI expression in vivo as well as in vitro. Presumably, the other three predicted Sp1-binding motifs46 were responsible for these effects. Our findings with the use of plasmid promoter constructs (Fig. 1B) also suggest that inhibition of histone deacetylases by sodium butyrate can lead to enhanced PIGM transcription through binding of Sp1 (and to a lesser degree of other transcription factors) to its cognate promoter motifs in its acetyl-modified form. This hypothesis is in line with previous reports showing that inhibition of histone deacetylases, as well as histone hyperacetylation, can lead to increased transcriptional activity through acetyl modification and increased affinity binding of Sp1.16,17

Regulation of acetylation and PIGM transcription by Sp1 might be important during embryonic and fetal development, when increased acetylation is required for coordinate expression of numerous genes. In this way, maintenance of an open chromatin configuration by histone acetylation would increase PIGM transcription and expression of GPI-linked proteins critical for neural development18,19 to levels sufficient to prevent lethal neurodevelopmental defects, such as those seen in female mice with a deleted Piga gene20 but inadequate to prevent severe epilepsy. We show that manipulation of acetylation in postnatal life with sodium phenylbutyrate can have a dramatic therapeutic effect on otherwise intractable seizures. The enhancing effect of sodium butyrate on PIGM mRNA and surface GPI expression on blood cells in vivo suggest that restoration of GPI biosynthesis in the central nervous system is responsible for the drug’s clinical effects. However, since direct assessment of primary neural tissue was not possible, it cannot be ruled out that the neurologic improvement was caused by alternative actions of sodium phenylbutyrate on the central nervous system. Sodium valproate is an antiepileptic agent with properties of a histone deacetylase inhibi-
tor and could have contributed to seizure control, along with sodium butyrate. Indeed, in our in vitro assays using concentrations of sodium valproate similar to the in vivo therapeutic range, we observed mild restoration of GPI expression in the patient’s lymphoblastoid cell line but no synergistic or additive effect with sodium butyrate (data not shown). Presumably, these levels are not sufficient for control of epilepsy in vivo.

Whether treatment with sodium phenylbutyrate eliminates or reduces the risk of thrombosis in inherited GPI deficiency is not known. Thrombosis is the only clinical feature shared by inherited GPI deficiency and paroxysmal nocturnal hemoglobinuria; in the latter, the lack of CD59, an inhibitor of membrane-attack complex of complement, is thought to lead to hypercoagulable platelets and contribute to an increased risk of thrombosis. In inherited GPI deficiency, 30 to 50% of platelets are CD59-deficient. However, sodium phenylbutyrate had no effect on the level of CD59 expression on platelets (data not shown), despite increasing granulocyte CD59 expression.

In summary, we have shown that the mutation responsible for inherited GPI deficiency disrupts an Sp1-dependent butyrate response element and is associated with hypoacetylation at the promoter of PIGM. Modification of acetylation with sodium butyrate enhances transcription of PIGM and surface GPI expression in vivo as well as in vitro and is of great therapeutic value. Therefore, sodium butyrate may be an effective therapeutic option for other diseases caused by Sp1-dependent hypoacetylation.

Dr. Almeida is a Leukaemia Research Fund Clinical Research Fellow, and Dr. Karadimitris is a Leukaemia Research Fund Bennett Senior Fellow. Drs. Murakami, Maeda, and Kinoshita are supported by grants from the Ministry of Education, Culture, Science, Sports, and Technology of Japan. Equipment was donated to the investigators by INADA.

No potential conflict of interest relevant to this article was reported.

We thank Dr. Richard Szydlo for performing the statistical analysis.

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Fecal Incontinence in Adults

Arnold Wald, M.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 author’s clinical recommendations.

A 53-year-old otherwise healthy woman presents with a 2-year history of intermittent fecal incontinence. Because of embarrassment, she has curtailed her social and professional activities. Physical activity often precipitates an episode, and she wears absorbent pads. She has occasional urinary incontinence when she coughs or sneezes. There is no history of gastrointestinal or rectal surgery and no neurologic symptoms. Physical examination reveals no perianal deformity or rectal prolapse. The tone of the anal canal is adequate, whereas contractions of the anal sphincter muscle and the puborectalis muscle are weak. On the patient’s bearing down, there is no rectal prolapse, and the perineal descent is approximately 2 cm. How should she be evaluated and treated?

The Clinical Problem

Fecal incontinence is a devastating nonfatal illness, resulting in considerable embarrassment and anxiety in those who have it. It affects 2 to 17% of people living in the community and almost half of all nursing home residents.1 Many affected persons do not voluntarily report fecal incontinence to their physicians and must be asked about it directly.2

The prevalence of fecal incontinence is increased among women, the elderly, persons with poor health status or physical limitations, and those residing in nursing homes.2 Other risk factors associated with fecal incontinence in adults include rectal radiation therapy (e.g., for prostate cancer), pregnancy, injury to the sphincter or nerve damage associated with vaginal delivery, anorectal surgical procedures (e.g., sphincterotomy for anal fissures), diarrhea alone or in association with the irritable bowel syndrome, and fecal impaction. Neurologic conditions (e.g., stroke, multiple sclerosis, spinal cord injury, and Parkinson’s disease) and diabetes are also risk factors.

Continence relies on the appropriate functioning of the puborectalis muscle and the internal and external anal sphincter muscles, which encircle the anal canal (Fig. 1). Factors such as stool consistency, rectal and colonic storage capacity, perception of rectal sensation, and cognitive and behavioral functioning also play important roles. An abnormality in any of these factors may result in fecal incontinence.

Strategies and Evidence

Evaluation

A detailed history should be taken to assess the frequency, severity, and nature of the incontinence and the effect of incontinence on the quality of the patient’s life, including an assessment of the patient’s ability to leave the house for work and social activities. Patients are particularly anxious about the unpredictability of episodes of fecal incontinence and often alter their social and professional activities to avoid embar-
rassment. An emphasis on only the frequency and type of episodes will result in underestimation of the often profound effect of this disorder on the quality of life. Although a number of incontinence scales have been developed, none are routinely used in practice.3,4

Physical examination should include perianal inspection, digital rectal examination, and a focused examination of the perineum. The assessment of the perineum and the digital anorectal exam are best performed while the patient is in the left lateral or prone position.5,6 The inspection may reveal prolapsed hemorrhoids, a patulous anus (indicative of denervation), anal deformity, or dermatitis resulting from frequent soiling. Excessive perineal descent (≥3 cm) or rectal prolapse may be identified by asking the patient to strain as if to defecate (optimally in the squatting position). Perineal sensation is determined by lightly touching the perianal skin with a cotton-tipped stick; the anocutaneous reflex (a brief contraction of the external anal sphincter when the perianal skin is lightly stroked) indicates the presence of intact sensory and motor innervation.

The digital rectal examination has been dismissed by some as inaccurate for assessing anal sphincter tone and strength.4 As with any such test, accuracy depends on the skill of the examiner. When performed by an experienced and knowledgeable examiner, the following features can be assessed or identified: anal-canal tone, contraction of the external anal sphincter, contraction of the puborectalis muscle, fecal impaction or mass, and disruptions of the anal sphincter. In one study, the positive predictive value of digital examinations performed by experienced clinicians to identify low resting pressure and squeeze pressure was 67% and 81%, respectively.7 Figure 1 depicts a proper digital rectal examination in a patient with fecal incontinence.
Diagnostic Testing
After fecal impaction with overflow, decreased rectal storage capacity, and neurologic causes have been ruled out (Table 1), and when there is diagnostic uncertainty after the history taking and physical examination, tests to assess anorectal structure and function may be useful (Table 2). Anorectal manometry is helpful to assess anal-sphincter tone and strength as well as the perception of rectal sensation. When a potentially reparable anal-sphincter disruption is a consideration, anal sonography is useful to assess the structural integrity of the sphincters. When a sphincter tear is discovered, assessment of the external anal sphincter and the puborectalis muscle with electromyography (EMG) is warranted to rule out concurrent denervation (which clinical experience suggests may reduce the chances of surgical success). These tests are best performed at tertiary care centers by experienced practitioners.

The value of measurement of pudendal-nerve terminal motor latencies (a measurement of conduction time through the terminal portion of the pudendal nerve to the external anal sphincter) and of barium proctography is more controversial. Dynamic pelvic magnetic resonance imaging (MRI) may provide information about the pelvic-floor anatomy and function, but pelvic MRI is costly and not widely available at present, and its precise role in the assessment of anorectal structure and function has not been established.

Management
Fecal incontinence after the age of 4 years should never be considered normal or age-appropriate. Management of the disorder should be tailored to the specific cause when possible, but typically a variety of strategies are used. These include modification of stool consistency and delivery of stool to the anorectum, behavioral interventions, and surgery to correct abnormal continence mechanisms. There are few randomized, controlled tri-
als, and management of fecal incontinence is guided by expert opinion, clinical experience, and case series. Referral to a specialist is not necessary in all cases, but it is warranted when conservative measures fail or when there may be a surgically correctable lesion.

**General Measures**

Incontinence pads protect the skin and prevent the soiling of clothing and bedding; polymers are used to conduct moisture away from the skin. Randomized trials indicate that disposable products are superior to nondisposable products in providing skin protection. Although not rigorously studied, barrier creams such as zinc oxide and menthol lotion (Calmoseptine) may prevent skin irritation. Topical antifungal agents are useful for perianal fungal infections.

**Medical and Pharmacologic Treatments**

In patients with overflow incontinence associated with fecal impaction, disimpaction and colon cleansing with large-volume warm-water enemas or oral polyethylene glycol with electrolyte solutions provide immediate relief. Such patients require an ongoing program of bowel management to prevent recurrence. Such programs involve regularly scheduled defection with the assistance of laxatives such as magnesium salts or polyethylene glycol or stimulant laxatives as rescue therapy if defection does not occur spontaneously within 3 days. Short-term (3 to 6 months) success rates of 60 to 80% have been reported in case series, but ongoing vigilance is required because of the high rates of recurrence.

When fecal incontinence is associated with decreased colonic and rectal storage capacity or with chronic diarrhea, treatment is directed toward reversing the underlying causes or, if this is not an option, modifying the volume, consistency, and delivery of stool (Table 3). Although trials of modified dietary intake of fiber are lacking, clinical experience suggests that in some patients, reducing the intake of dietary fiber has benefit when combined with the administration of antidiarrheal drugs, which slow colonic transit and decrease intestinal fluid secretion. Of the antidiarrheal agents, loperamide (Imodium, Ortho–McNeil) is preferred because it has no effects on the central nervous system, has been shown in a randomized, controlled trial in patients with fecal incontinence to be more effective than diphenoxylate–atropine (Lomotil, Searle), and may increase intraluminal anal sphincter tone. Adequate dosing and the timing of administration are important (2 to 4 mg administered 45 minutes before meals or before social occasions) to avoid accidents outside the home. In patients with diarrhea associated with the irritable bowel syndrome, tricyclic agents may also help to alleviate diarrhea by means of their anticholinergic properties. Continence is more easily established for solid than for liquid stools and gas, especially when there is adequate puborectalis muscle function. Alosetron (Lotronex, GlaxoSmithKline) is a 5-hydroxytryptamine type 3 antagonist that has been approved by the Food and Drug Administration for women with the irritable bowel syndrome and diarrhea; because the drug reduces urgency and the frequency of liquid stool, it may improve fecal incontinence caused by other conditions, although this hypothesis has not been formally tested. Because of cost considerations, as well as reports of ischemic colitis, the use of alosetron should be considered only after treatment with other antidiarrheal medications has failed.

Patients with internal anal sphincter abnormalities that cause decreased tone in the anal canal characteristically also have fecal soiling with normal bowel habits. Clinical experience suggests that an anal plug constructed of cotton balls may be an inexpensive approach to restore the passive barrier function and may also serve as an absorbent, although this approach has not been formally studied.
Biofeedback
In contrast to the use of exercises to strengthen the pelvic floor muscle (Kegel exercises), biofeedback has been used to improve the perception of rectal sensation and the responsiveness of the sphincter muscle to balloon distention with the use of instruments that monitor sphincter contractions. Although several case series have reported the efficacy of biofeedback, these studies lacked sham controls, often had imprecise end points, and were subject to bias. Randomized, controlled, blinded trials have failed to show the superiority of biofeedback to conservative measures, such as instruction on managing fecal incontinence, implementing lifestyle modifications, obtaining emotional support, and using medications and dietary changes to modify the liquidity and delivery of stool. Neither was instrumental feedback superior to noninstrumental feedback, which used simple digital insertion, providing the patient only tactile feedback.

Surgical Approaches
Anal sphincteroplasty is based on the repair of an anatomically disrupted anal sphincter and is best performed with the use of a technique that overlaps the two ends of the sphincter muscles. Anal sonography to identify sphincter disruptions has replaced EMG mapping of the external anal sphincter. Although overlapping sphincteroplasty is highly effective in acute sphincter disruption, its durability and effectiveness in patients with nonacute sphincter disruption are less certain. Many reports have noted a short-term improvement in fecal continence in up to 85% of patients, but failure rates of approximately 50% have been noted after 5 years of follow-up. In several case series, fecal continence after sphincteroplasty was maintained in only 28% of patients followed for a mean of 40 months and in only 11 to 14% of those followed for more than 69 months.

The criteria for selecting patients who can benefit from sphincter repair remain uncertain. On the basis of case series, the clinical features that may predict treatment failure include an internal anal sphincter defect, prolonged pudendal-nerve terminal motor latency (although this finding has been inconsistent), atrophy of the external anal sphincter on pelvic MRI, and the irritable bowel syndrome. However, prospective data are lacking to confirm these findings. In view of the potential complications of surgery and the questionable durability of modest clinical improvements, a reasonable approach is to perform surgery in selected cases.

Table 3. Suggested Approaches to Treatment of Fecal Incontinence in Adults.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overflow</td>
<td>Disimpaction</td>
</tr>
<tr>
<td></td>
<td>Colon evacuation</td>
</tr>
<tr>
<td></td>
<td>Periodic defecation (twice weekly) with the use of laxatives, enemas, or both, if necessary</td>
</tr>
<tr>
<td>Decreased storage capacity</td>
<td>Low-fiber diet</td>
</tr>
<tr>
<td></td>
<td>Loperamide†</td>
</tr>
<tr>
<td></td>
<td>Periodic defecation (twice weekly) with or without the use of laxatives</td>
</tr>
<tr>
<td>Isolated internal anal sphincter weakness</td>
<td>Loperamide†</td>
</tr>
<tr>
<td></td>
<td>Anal cotton plug</td>
</tr>
<tr>
<td>Anal sphincter disruption</td>
<td>Loperamide†</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Sacral-nerve stimulation‡</td>
</tr>
<tr>
<td>Behavioral problems or dementia</td>
<td>Prompted defecation with regular use of laxatives, suppositories, or enemas (twice weekly); administration of loperamide in the presence of diarrhea or between enemas</td>
</tr>
</tbody>
</table>

* For fecal incontinence from all causes, general measures include skin care, the use of incontinence pads, odor control, and support from caregivers, as needed.
† The suggested dose of loperamide is 2 to 4 mg administered in the morning or twice daily, as needed, or 2 to 4 mg 45 minutes before travel to locations where toilet facilities are not readily available. There is no use of the drug on days of induced defecation.
‡ This method is not approved in the United States for fecal incontinence.
patients only when nonsurgical measures prove unsatisfactory.

Antegrade colonic irrigation by means of an appendicostomy or cecostomy was initially developed to treat fecal incontinence in children but has also been used in adults. Access to the cecum is established by externalizing the appendix or by implanting a cecostomy button surgically or by percutaneous colonoscopy (similar to placement of a gastrostomy tube) in adults and children. Large-volume enemas can be delivered into the cecum with the use of a catheter that is passed through the cecostomy stoma daily or every other day in order to empty the colon completely to prevent fecal soiling. Complications include traumatic catheterization with perforation, stomal stenosis, and infection, but these have become less frequent as the procedure has been simplified. In a recent review of studies of adults undergoing this procedure, stenosis developed in 20% of the patients, and in 14% the procedure was reversed because of leakage or abdominal pain during the administration of enemas. Optimal candidates are those with neurogenic fecal incontinence or anorectal deformities. Infrequently, surgery may also be performed to replace a damaged or nonfunctioning anal sphincter complex with the use of nearby muscles and the implantation of a stimulator (dynamic graciloplasty) or an artificial sphincter. Improved fecal continence has been reported in more than 50% of the patients in whom the surgery is performed. However, complication rates have been as high as 42%, including infections, device malfunctions, and in the case of implantation of an artificial sphincter, explantation of the device. Such procedures are best performed by experienced surgical teams.

In the absence of demonstrable anal sphincter defects, the efficacy of surgical approaches designed to correct abnormalities of the pelvic floor, such as anterior levatorplasty and total repair of the pelvic floor, is uncertain. For severe incontinence refractory to other approaches, clinical experience suggests that a diverting colostomy may provide substantial improvement in a majority of patients, although the effects on the quality of life have not been rigorously evaluated in a prospective, longitudinal study.

Stimulation of the Sacral Nerve
The use of stimulation of the sacral spinal nerve for treatment of fecal incontinence derives from its successful use in treating disorders of urinary voiding and continence. The procedure involves three phases: the location of the sacral spinal nerves on percutaneous probing with a needle electrode to identify the nerve root that maximally stimulates anal sphincter contraction, temporary placement of an electrode for stimulation of the nerve root identified on testing as the most efficient, and permanent implantation of a neurostimulator for long-term therapeutic stimulation.

In the approximately 90% of patients in whom the procedure is attempted and in whom the first two phases of the therapy are successfully completed, clinical improvement of fecal incontinence has been confirmed in studies with follow-up of 24 months or less with full restoration of fecal continence in 37% to 74% of these patients. Objective physiological changes include increases in both resting pressure and squeeze pressure, increased squeeze durations, and improved perception of rectal sensation. In a multicenter trial involving 37 patients, adverse events included pain (26%), which often resolved after the stimulator was reprogrammed or repositioned; lead breakage (3%); and infection (3%).

Areas of Uncertainty
Data from randomized trials are lacking to guide the optimal approach to the diagnosis and treatment of fecal incontinence. Kegel exercises and biofeedback are often recommended, since they are without risk; biofeedback, however, is costly and time-consuming and has not been shown to be effective in randomized trials assessing its use. Effects of modification of fiber intake on fecal incontinence have also not been carefully evaluated. Randomized trials comparing surgical with nonsurgical interventions or comparing different surgical approaches are also lacking, and data on surgical outcomes are derived largely from retrospective case series. It is speculated that sacral-nerve stimulation may be beneficial after anal sphincteroplasty when the results of surgery are suboptimal and include partial denervation of the puborectalis, the external anal sphincter, or both; however, data are lacking to confirm this possibility.

Guidelines
Practice guidelines for fecal incontinence based on expert opinion have been published by the American College of Gastroenterology (ACG). For
the most part, these recommendations are similar to those contained in this review. One exception is that the AGA guidelines recommend biofeedback, but in the absence of supporting evidence from randomized clinical trials.

SUMMARY AND RECOMMENDATIONS

Careful history taking and physical examination often reveal the cause or causes of fecal incontinence in adults; further testing is warranted when there is diagnostic uncertainty. In most patients, overflow, impaired colorectal storage capacity, and isolated internal anal sphincter weakness can be identified on the basis of the history and examination. When the cause of fecal incontinence remains uncertain, such as in the case of the patient described in the vignette, the choice of testing will vary according to institutional expertise and availability, but I would proceed with anorectal manometry and anal sonography (or pelvic MRI). If an external sphincter tear is found, EMG of both the puborectalis muscle and the external anal sphincter may help guide therapeutic decisions; outcomes of surgical repair appear to be better in the absence of denervation, although long-term success rates are suboptimal even in these cases. If no surgically remedial lesion is identified, I would recommend the use of disposable incontinence pads and measures to reduce stool delivery to the rectum, including the administration of loperamide (2 to 4 mg 45 minutes before planned activities or travel) and reduced fiber intake, although this approach has not been rigorously evaluated. I would also suggest Kegel exercises to strengthen the puborectalis muscle and external anal sphincter, given their possible benefit and lack of risk, although there is also no rigorous evidence to support their benefit. Because data supporting the efficacy of sacral-nerve stimulation (which is not yet approved in the United States for fecal incontinence) are limited, this approach should be considered where it is available and for patients whose condition does not respond to conservative measures.

Dr. Wald reports receiving consulting fees from Boehringer Ingelheim, Microbia, and Novartis, lecture fees from Novartis, and grant support from Microbia. No other potential conflict of interest relevant to this article was reported.

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The Journal’s Web site (www.nejm.org) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronologic order, with the most recent first.


Copyright © 2007 Massachusetts Medical Society.
A 64-YEAR-OLD WOMAN WITH ULCERATIVE COLITIS PRESENTED WITH ABDOMINAL PAIN. Plain radiography of the abdomen showed dilatation of the large bowel with a plug of barium (Panel A, arrow) and a second plug in the pelvis. The patient’s last barium study, performed 9 months earlier, had been normal. Abdominal computed tomographic examination for strictures and underlying masses showed a short segment of thick-walled left colon immediately distal to the plug of barium in the abdomen (Panel B, arrow). The plug in the pelvis was found to be in the cecum and was not associated with small-bowel obstruction. The patient underwent a colonic wash under general anesthesia, followed by colonoscopic visualization of the inspissated barium, which was dissolved with a high-pressure jet stream of water. The large-bowel obstruction resolved, and colonoscopy a month later up to the terminal ileum showed no colonic strictures or residual barium plugs.

Inspissation of barium can be minimized by keeping the patient well hydrated. If there is a history of constipation, patients should be encouraged to use a stool softener after a barium meal.

Copyright © 2007 Massachusetts Medical Society.
A 56-year-old woman with a history of primary pulmonary hypertension and heart and lung transplantation was admitted to the hospital because of renal failure. When the patient was approximately 43 years old, a diagnosis of primary pulmonary hypertension was made at another institution; progressive hypoxemia and polycythemia developed, and 3 years later (10 years before admission), heart and lung transplantation was performed at another hospital. The patient’s symptoms improved, and oxygenation and hemoglobin levels returned to normal. Her medications included prednisone (10 mg daily), cyclosporine (225 mg twice daily), azathioprine (75 mg per day in divided doses), folate, hydralazine, furosemide, nifedipine, potassium sulfate, aluminum hydroxide, and trimethoprim for intermittent urinary tract infections.

During the next 10 years, the patient was followed by specialists in cardiology, pulmonary medicine, transplantation surgery, and nephrology. The levels of urea nitrogen and creatinine gradually rose, and proteinuria developed; urinalyses disclosed no increase in red or white cells or casts (Table 1). Seven months before admission, indirect immunofluorescence testing for antineutrophil cytoplasmic antibodies (ANCA) and an enzyme-linked immunosorbent assay for antibodies to p29 (proteinase 3) and to myeloperoxidase were negative. A test for antinuclear antibodies was positive at 1:160, with a speckled pattern. Ultrasonographic examination of the kidneys showed increased echotexture bilaterally. The right kidney was 10.5 cm in length and the left 8.7 cm. There was no evidence of hydronephrosis. The cyclosporine level was 239 ng per milliliter. Three months before admission, the erythrocyte sedimentation rate was 57 mm per hour (normal range, 1 to 25). The patient was admitted to this hospital for further evaluation.

A heart murmur had been diagnosed when the patient was 3 years old, but no treatment was given and her activities were not restricted. When she was 19 years old, pedal edema and proteinuria developed, and a diagnosis of glomerulonephritis was made at another hospital; corticosteroid therapy was prescribed, and the edema resolved. Corticosteroids were discontinued after 3 years, and her renal function was reportedly normal. Low-grade proteinuria occurred intermittently thereafter, with normal levels of urea nitrogen and creatinine. When the patient was 31 years old, the results of an antinuclear antibody test were positive; when she was 34 years
old, essential hypertension was diagnosed and treated with meditation and propranolol. The patient had had sporadic gastrointestinal symptoms attributed to spastic colon. Tonsillectomy and adenoidectomy had been performed at a young age, incidental splenectomy during laparotomy for an unspecified problem 17 years before the current admission, salpingectomy and laparotomy with lysis of adhesions because of a small-bowel obstruction 1 year before admission, and left hemithyroidectomy for a benign nodule 6 months before admission. She was allergic to penicillin, sulfa drugs, diphenhydramine, oxycodone, and meperidine.

The patient’s father had had hypertension and coronary artery disease and had died at the age of 78 years, and her mother had diabetes; her 25-year-old daughter was in good health. She did not smoke tobacco; she drank alcohol occasionally. On admission, her medications included cyclosporine, azathioprine (75 mg per day in divided doses), prednisone (5 mg per day), nifedipine, thyroxine, calcitriol, trimethoprim, oral clotrimazole, folic acid, calcium carbonate, multivitamins, and vitamin A; pneumococcal vaccine had been administered after her splenectomy.

On examination, the blood pressure was 130/80 mm Hg, the pulse 90 beats per minute, the temperature 36.4°C, and the oxygen saturation 99% when the patient was breathing ambient air. There was a well-healed scar over the sternum. The lungs were clear; there was a grade 2/6 systolic cardiac murmur and 1+ to 2+ edema of the hands and lower legs. Results of the remainder of the examination were normal. The complete blood count and levels of serum electrolytes, liver-function tests, and levels of total protein and albumin were normal. Results of other laboratory tests are shown in Table 1.

A diagnostic procedure was performed.

### Table 1. Results of Laboratory Tests.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range in Adults†</th>
<th>Before Transplant (10 yr before admission)</th>
<th>9 Yr before Admission</th>
<th>7 Yr before Admission</th>
<th>2 Yr before Admission</th>
<th>7 Mo before Admission</th>
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* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. These ranges may therefore not be appropriate for all patients.
Differential Diagnosis

Dr. Nelson B. Goes: This patient presented with chronic kidney disease 10 years after successful heart–lung transplantation for idiopathic pulmonary hypertension. She had a history of intermittent urinary tract infections and a remote pretransplantation history of glomerulonephritis, with subsequent intermittent, low-grade proteinuria (non-nephrotic range) and normal urea nitrogen and creatinine levels (creatinine, 3.2 mg per deciliter [282.9 μmol per liter], creatinine clearance 21 ml per minute). She had a low positive titer on antinuclear antibody testing, negative results on ANCA testing, and an ultrasound showing asymmetry of the kidneys, increased echogenicity, and no evidence of hydronephrosis. Chronic kidney disease is categorized in five stages that are based on the estimated glomerular filtration rate, with stage 1 representing mild disease, and stage 5 kidney failure. According to this classification, the patient has stage 4 disease, a stage at which dialysis is likely to be required within a year and kidney transplantation needs to be considered.

Chronic Kidney Disease in Nonrenal Solid-Organ Transplantation

Chronic kidney disease is a common complication of nonrenal solid-organ transplantation. At 5 years, the cumulative incidence of chronic kidney disease is highest among recipients of intestine allografts (21.3%), followed by recipients of liver (18.1%), lung (15.8%), heart (10.9%), and heart–lung (6.9%) allografts. The risk continues to increase with the interval since transplantation. This patient, who received a heart–lung transplant 10 years ago, is at high risk for the development of chronic kidney disease.

In one study, 29% of patients with chronic kidney disease after nonrenal solid-organ transplantation required renal replacement therapy. Chronic kidney disease increases the risk of death by a factor of 4 among recipients of nonrenal solid-organ transplants. Several factors are associated with chronic kidney disease in such patients, including female sex, older age, immunosuppressive treatment with calcineurin inhibitors, low glomerular filtration rate, presence of acute renal failure before or at the time of transplantation, and need for dialysis. The presence of underlying chronic renal disease may be missed in patients thought to have renal disease because of the failure of other organs (e.g., patients with very low cardiac output who are awaiting heart transplantation or those with the hepatorenal syndrome who are awaiting liver transplantation). The presence of hypertension and diabetes is associated with an increased risk of chronic kidney disease. More recent recipients of nonrenal solid-organ transplants are less likely to have chronic kidney disease, possibly because of more judicious use of immunosuppressive agents. Although the differential diagnosis in this case includes all causes of chronic kidney disease, I will specifically consider diseases that are common among patients who receive transplants (Table 2).

Diabetic and Hypertensive Nephropathy

Diabetes mellitus is an important complication of transplantation that contributes to chronic kidney disease. Weight gain is probably the most important factor predisposing patients to the development of diabetes mellitus after transplantation. The risk is also increased by exposure to corticosteroids and the calcineurin-inhibitor agents (cyclosporine and tacrolimus). Hypertension occurs in 80% of transplant recipients, is also related to the use of calcineurin inhibitors and corticosteroids, and may cause chronic kidney disease, as can some of the underlying disease processes that lead to end-stage organ failure necessitating transplantation, such as hepatitis C and amyloidosis.

Glomerular Disease

Could this patient have had a glomerular disease? At the age of 19 years, she had the nephrotic syndrome, but there was apparently no histologic diagnosis. She could have had minimal-change disease. She also could have had membranous glomerulonephritis, which is the most common cause of the nephrotic syndrome in white adults and can have a very long and indolent course with relatively preserved renal function. Indeed, about 25% of patients with membranous glomerulonephritis have a spontaneous remission. Could she have had systemic lupus erythematosus and lupus nephritis? At the age of 34 years, she had systemic and pulmonary hypertension, which can be complications of lupus. However, despite low antinuclear antibody titers on two occasions, she did not have other features of lupus.
This patient, who was taking multiple medications and had multiple urinary tract infections, is at high risk for the development of chronic tubulointerstitial disease. She could have had undiagnosed episodes of pyelonephritis. She did not have exposure to nonsteroidal antiinflammatory agents. Transplant recipients have close follow-up and are typically compliant, so I would not expect her to have taken over-the-counter medications without her physicians’ knowledge. Obstructive nephropathy has to be considered in this patient; she had a history of abdominal operations, but the renal ultrasonographic studies are not consistent with this disorder. Physicians caring for patients with transplants have to consider tumors that can develop in the immunosuppressed state. Both cytomegalovirus and polyomavirus BK (BK virus) nephropathy can also occur in immunosuppressed patients. Although BK-virus nephropathy is almost exclusively found among renal transplant recipients, there are reported cases in recipients of heart, lung, and kidney–pancreas allografts.3–7

**Vascular disease**

In this patient, vascular diseases have to be considered not only because of her exposure to calcineurin inhibitors but also because of her history of pulmonary hypertension. She had no systemic features of scleroderma, and nothing suggested scleroderma in the native lung or allografts. She did not have systemic manifestations of vasculitis, but she could have had vasculitis limited to the kidneys. Hydralazine has been associated with Wegener’s granulomatosis, but ANCA test results were negative; since these tests are very reliable, Wegener’s granulomatosis is unlikely in this case.8

Thrombotic microangiopathy and the hemolytic–uremic syndrome are well-known complications of calcineurin inhibitors. The normal, stable platelet count in this patient would not support these diagnoses. She could have had isolated renal thrombotic microangiopathy with no systemic features, which is a possibility that I will keep in the differential diagnosis. Anticardiolipin or lupus anticoagulant antibodies can be seen in transplant recipients and contribute to thrombotic microangiopathy. This patient had asymmetrical kidneys and elevated cholesterol levels, and her immunosuppressed state increases the likelihood of renal-artery stenosis. Indeed, vascular complications (myocardial infarcts and strokes) are the main cause of death among transplant recipients.

**Complications of Immunosuppressive Drugs**

One has to consider immune and nonimmune complications of immunosuppressive drugs in the assessment of chronic kidney disease in patients who have undergone nonrenal solid-organ transplantation.9 The immune complications of immunosuppression include cancer and infections. Among malignant tumors, there is a predisposition to virus-related cancer, such as that in the skin and cervix, and to virus-related lymphoproliferative disorders. Although post-transplantation lymphoproliferative disease can develop in renal allografts, it is unlikely that both native kidneys would be involved after nonrenal transplantation. Finally, this patient’s renal disease was indolent, developing over many years. All these factors make renal post-transplantation lymphoproliferative disease unlikely.

Nonimmune side effects occur with most immunosuppressive agents as well. Azathioprine, one of the oldest, is an antimetabolite that has toxic effects on the bone marrow and the liver.
sine monophosphate dehydrogenase inhibitors, mycophenolate mofetil and mycophenolic acid, target T and B lymphocytes, since in contrast to all other cells in the body, lymphocytes lack an alternative pathway for synthesis of purines. These agents may cause anemia, leukopenia, and diarrhea, but they have not been associated with renal failure.

Calcineurin Inhibitors
The introduction of treatment with the calcineurin inhibitors, cyclosporine and tacrolimus, caused a revolution in the field of transplantation, making transplantation of lungs, heart, pancreas, and liver possible. These prodrugs cross the cytoplasmic membrane; cyclosporine binds cyclophilin and tacrolimus binds FKB12, forming complexes that prevent calcineurin from dephosphorylating the nuclear factor of activated T cells and preventing activation of target genes such as IL2. Both agents can cause hypertension, nephrotoxicity, the hemolytic–uremic syndrome, thrombotic microangiopathy, and diabetes.\textsuperscript{10-12} Calcineurin inhibitors also cause hyperlipidemia, which this patient had (Table 1). Hyperuricemia and neurotoxicity are also seen. The likely mechanisms of action include increasing peripheral vascular resistance\textsuperscript{5} and up-regulation of profibrogenic genes such as the gene for transforming growth factor β.\textsuperscript{8,13} Calcineurin nephrotoxicity may be acute or chronic. Acute nephrotoxicity may be associated with renal thrombotic microangiopathy or the hemolytic–uremic syndrome, and it causes a reduction in the glomerular filtration rate (which is usually reversible) and hyperkalemia. Glomerulosclerosis may occur and is usually associated with high-grade arteriolar hyalinosis and vascular narrowing. Both focal segmental glomerulosclerosis and diffuse glomerulopathy have been associated with long-term use of calcineurin inhibitors.\textsuperscript{11,12} They are also associated with fibrosis of the renal interstitium. This patient had been taking cyclosporine for 10 years and had evidence of toxicity in the form of hyperlipidemia; the presence of slowly rising creatinine and non–nephrotic-range proteinuria is not typical for a glomerular process, but it does fit well with the course of chronic interstitial nephritis caused by exposure to calcineurin inhibitors.

TOR Inhibitors
Target of rapamycin (TOR) inhibitors block the cell cycle through their action on the intracytoplasmic protein TOR. There are two agents in this class, sirolimus and everolimus. Both are known to cause bone marrow suppression, hyperlipidemia, and delayed wound healing, and in renal-transplant recipients they prolong the period of recovery after episodes of acute tubular injury. Most patients who present with these complications recover shortly after these drugs are stopped. Acne, mouth ulcers, gastrointestinal symptoms, peripheral edema that can be asymmetric and is not associated with the nephrotic syndrome or congestive heart failure, venous thrombosis, and some degree of nephrotoxicity may occur. However, this patient was not taking a TOR inhibitor.

In conclusion, I believe that this patient's chronic kidney disease was induced by calcineurin inhibitors, specifically, cyclosporine. The diagnostic procedure should be a renal biopsy.

Dr. Nancy Lee Harris (Pathology): Dr. Bazari, would you summarize your thinking at the time that you saw this patient?

Dr. Hasan Bazari (Nephrology): She had progressive renal disease characterized by marked but non-nephrotic proteinuria, and like Dr. Goes, I thought that her condition was probably due to cyclosporine toxicity. One could speculate that she had secondary focal sclerosis. The question of whether her primary disease could have recurred is always in the background. We wondered about either membranous or focal and segmental glomerulosclerosis as the underlying preexisting diagnosis, but since her condition had been stable for years and chronic kidney disease occurred in the setting of exposure to a calcineurin inhibitor, we favored the diagnosis of cyclosporine toxicity. We performed a renal biopsy.

Clinical Diagnosis
Chronic kidney disease induced by the calcineurin inhibitor cyclosporine.

Dr. Nelson B. Goes's Diagnosis
Chronic kidney disease induced by the calcineurin inhibitor cyclosporine.

Pathological Discussion
Dr. Robert B. Colvin: A renal biopsy was performed, and 1 year later, after end-stage renal disease had developed, a nephrectomy was performed, with
transplantation of a kidney from an unrelated living donor. Examination of the kidney by light microscopy showed widespread collapse of glomeruli and marked hyperplasia of podocytes, with reabsorption droplets, segmental and global scarring, hyalnosis, and adhesions (Fig. 1A and 1C). The glomerular basement membrane was normal on periodic acid–Schiff staining (Fig. 1C). A geographic distribution of the sclerosis (e.g., by vascular tree or corticomedullary junction) was not evident. Tubules showed marked focal dilatation with proteinaceous casts, reactive epithelial cells, and “anoikis” (or sloughing of epithelium—derived from the Greek word for “homeless”) (Fig. 1B). Occasionally tubules had neutrophils, but there was no other evidence of pyelonephritis, and this is a common finding in end-stage kidney disease. Podocyte proliferation was evident on immunoperoxidase staining for Ki67 (Fig. 1D). A nodular interstitial mononuclear infiltrate is present. Arteries are characterized by severe intimal fibrosis, which I would attribute to the long-standing hypertension. There is marked hyalinosis of arterioles, often circumferential and sometimes nodular on the external aspect of the arteriole—a feature of calcineurin-inhibitor toxicity (Fig. 1A, 1E, and 1F). Several arterioles are occluded by hyaline and foam cells (Fig. 1A and 1F).

Immunofluorescence shows segmental IgM and C3 deposition in glomeruli. Electron microscopy shows widespread effacement of foot processes (Fig. 2A), with no deposits except for hyaline and no tubuloreticular structures. The glomerular basement membrane shows abundant newly formed subepithelial laminations where the podocytes are separated from this membrane (Fig. 2B). The endothelial cells are reactive and have lost fenestrations.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS, COLLAPSING VARIANT

The glomerulonephritis that the patient had at the age of 19 years resolved, and it is not related to the current disease. Instead, the glomerular changes are typical of focal segmental glomerulosclerosis, which has five subtypes: collapsing, tip, cellular, perihilar, and not otherwise specified (or usual).† The presence of collapsed glomeruli and marked podocyte reaction puts this case into the collapsing category. The collapsing variant of focal segmental glomerulosclerosis (also known as collapsing glomerulopathy)* is a form of glomerular injury characterized by capillary collapse and visceral epithelial hypercellularity; it is often associated with nephrotic-range proteinuria and a rapid, progressive decline in renal function.†† Collapsing glomerulopathy is a pattern of injury that has several causes, including human immunodeficiency virus, treatment with pamidronate, heroin abuse, and parvovirus B-19 infection, but in a substantial number of cases there is no known cause. The common pathogenetic mechanisms are obscure, although hemodynamic disturbances, probably at the arteriolar level, are probably important in the pathogenesis of the collapsing lesions. The pathophysiological process that leads to this variant is believed to be dysregulation of the podocyte. Podocyte proliferation (not normally detectable) is typical of this disease, illustrated by the positive staining for Ki67 in this and other cases (Fig. 1D).

GLOMERULAR COLLAPSE AS A FORM OF CYCLOSPORINE TOXICITY

Could the collapsing glomerulopathy in this case be due to cyclosporine toxicity? Glomerular collapse has been noted both at autopsy and on biopsy in more than 50% of native kidneys in patients with nonrenal solid-organ transplants who were treated with cyclosporine. The development of focal segmental glomerulosclerosis (type not otherwise specified) has been reported in up to 30% of renal-transplant recipients taking cyclosporine who have chronic allograft nephropathy 6 months or more after transplantation. Finally, collapsing glomerulopathy has been described in renal allografts in patients taking cyclosporine and has been associated with a high rate of renal failure and graft loss.

In this case, I believe that the vascular disease is the probable basis of the glomerular change. The arteriolar lesions are probably due to a combination of chronic cyclosporine toxicity, hyperlipidemia, and hypertension. A component of thrombotic microangiopathy cannot be ruled out.

CYCLOSPORINE-MEDIATED ARTERIOLOPATHY

This case has features that are typical of chronic cyclosporine arteriolopathy, which is characterized by replacement of the degenerated smooth-muscle cells in the tunica media vasorum with hyaline deposits, which typically have a beaded pattern. The lesion begins and predominates in the afferent arterioles but may progress to the small arteri-
ies and efferent arterioles. This characteristic arteriolopathy has been found at autopsy in approximately half the native kidneys in patients treated with cyclosporine and in none of the patients who were not. Tacrolimus causes similar lesions.

This is the second case that we have seen at this hospital of collapsing glomerulopathy in the native kidney. The process is characterized by collapse of the glomerular tuft, with increased numbers of podocytes, which are enlarged and contain protein reabsorption droplets. Several podocyte nuclei are stained with a marker of cell proliferation. The arterioles show marked hyalinosis, sometimes with peripheral nodular replacement of smooth-muscle cells or transmural accumulation and the presence of foam cells in the intima that occlude the lumen.
Collapsing glomerulopathy, associated with severe hyaline arteriolopathy, probably caused by chronic cyclosporine toxicity (with other potential factors including hyperlipidemia and hypertension). Hypertensive arteriosclerosis.

Dr. Goes reports receiving consulting fees from Boehringer Ingelheim and grant support from Fujisawa Healthcare, and Dr. Colvin reports receiving grant support from the Roche Organ Transplant Research Foundation. No other potential conflict of interest relevant to this article was reported.

**Figure 2.** Electron Micrographs of the Renal-Biopsy Specimen.

Panel A shows widespread effacement of glomerular podocyte (arrowhead) foot processes, and Panel B shows lifting off of podocytes, with accumulation of subepithelial basement-membrane layers (arrowhead).

**ANATOMICAL DIAGNOSES**

Collapsing glomerulopathy, with severe hyaline arteriolopathy, probably caused by chronic cyclosporine toxicity (with other potential factors including hyperlipidemia and hypertension). Hypertensive arteriosclerosis.

**REFERENCES**


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LANTERN SLIDES UPDATED: COMPLETE POWERPOINT SLIDE SETS FROM THE CLINICOPATHOLOGICAL CONFERENCES

Any reader of the Journal who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is now eligible to receive a complete set of PowerPoint slides, including digital images, with identifying legends, shown at the live Clinicopathological Conference (CPC) that is the basis of the Case Record. This slide set contains all of the images from the CPC, not only those published in the Journal. Radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs, as well as unpublished text slides, tables, and diagrams, are included. Every year 40 sets are produced, averaging 50-60 slides per set. Each set is supplied on a compact disc and is mailed to coincide with the publication of the Case Record.

The cost of an annual subscription is $600, or individual sets may be purchased for $50 each. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or e-mail Pathphotoslides@partners.org.
Blood transfusion has for years been considered to have obvious clinical benefits and to be a relatively low-risk procedure. Not until the early 1980s did transfusion practices begin to come under systematic scrutiny. Initially, this trend was driven by concern about transfusion-related infection, particularly by human immunodeficiency virus, but advances in transfusion medicine have greatly decreased the risk of transmission of viruses by transfused blood. Now, other concerns — the effects of transfusion on the immune system, transfusion-related acute lung injury, and the age of transfused blood — drive the debate over transfusion practice and have led to methodical examinations of the benefits of transfusion. These new considerations are particularly important for critically ill patients.

Anemia is prevalent in critically ill adults, who as a group receive a large number of red-cell transfusions. By the third day in the intensive care unit (ICU), 95% of critically ill patients have anemia, and 40 to 50% of them will receive on average almost 5 units of red cells during their stay in the ICU. Despite the frequency of transfusion among the critically ill, the optimal treatment of anemia in euvolemic, critically ill patients remains controversial. Red-cell transfusion is commonly used in the critical care setting to increase oxygen delivery to tissues, especially in patients in shock. However, several studies have raised questions regarding the validity of the assumption that red-cell transfusion is beneficial for critically ill patients with anemia. Two plausible hypotheses could explain the apparent lack of benefit from such transfusions: immunomodulation and the "storage lesion," which consists of biochemical and molecular changes and an accumulation of inflammatory mediators that develop over time in stored red cells.

The best evidence concerning the efficacy of red-cell transfusion in critically ill patients is from the Transfusion Requirements in Critical Care (TRICC) trial. In this randomized, controlled study involving adults in critical care, a liberal transfusion strategy (target hemoglobin level, 10.0 to 12.0 g per deciliter, with a transfusion trigger of 10.0 g per deciliter) was compared with a restrictive transfusion strategy (target hemoglobin level, 7.0 to 9.0 g per deciliter, with a transfusion trigger of 7.0 g per deciliter) in a general medical and surgical setting. The restrictive group received 54% fewer red-cell units than did the liberal group, and the restrictive strategy was found to be at least as effective as the liberal strategy with respect to mortality. In patients who were less acutely ill (with a score of <20 on the Acute Physiology and Chronic Health Evaluation [APACHE II]) or under 55 years of age, the restrictive strategy was actually superior, since it was associated with a decrease in mortality, as compared with the liberal strategy.

Most of the information on red-cell transfusion in critically ill patients has come from studies in adults, but such transfusions are also frequently used in critically ill infants and children. A recent observational study found that 14% of children who were admitted to a pediatric intensive care unit (PICU) received at least one red-cell transfusion during their stay in the PICU. Determinants for transfusion were similar to those that have been reported in adults (anemia, cardiac disease, severity of illness, and multiple organ dysfunction), suggesting that the use of red-cell transfusion in children is similar to that in adults.
In this issue of the Journal, a study by Lacroix et al., called the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) trial, is a notable advance in the study of red-cell transfusion in children and has implications for understanding the role of such transfusions in all critically ill patients. The transfusion thresholds adopted by the investigators (7 g per deciliter vs. 9.5 g per deciliter) were similar to those used in the TRICC trial and produced a mean difference of 2.1 g per deciliter in hemoglobin level between the two study groups. Low death rates among patients in PICUs precluded the use of death as an end point, but multiple organ dysfunction was an appropriate and clinically meaningful primary outcome. Similar to the results in the TRICC trial, the restrictive strategy used in the TRIPICU trial was at least equivalent to the liberal strategy in the outcome of multiple organ dysfunction and was associated with a 44% reduction in the number of red-cell transfusions. Even with a conservative transfusion threshold (7 g per deciliter), nearly 50% of the children in the TRIPICU trial received a transfusion, which highlights the frequency of anemia in critical illnesses. Although the numbers of temporary protocol suspensions were relatively low, we wonder whether the suspensions were actually necessary or whether they were, as the authors suggest, a reflection of physicians’ discomfort in withholding transfusion rather than of a physiological need for more oxygen delivery.

The study by Lacroix et al. is consistent with recent data from the Premature Infants in Need of Transfusion (PINT) trial, in which 451 infants weighing less than 1000 g, who had a gestational age of less than 31 weeks and were less than 48 hours old, were randomly assigned to either a low-threshold group or a high-threshold group as a transfusion strategy. The primary outcome was a composite of in-hospital death, severe retinopathy, bronchopulmonary dysplasia, and brain injury as detected by cranial ultrasonography. There was no difference between the two groups in the composite outcome and no suggestion of a difference between them in the incidence of brain injury. However, Bell et al., in their single-center trial of restrictive versus liberal transfusion strategies in 100 hospitalized preterm infants (weight, 500 to 1300 g), found no differences in most outcomes, including survival, patent ductus arteriosus, retinopathy, and bronchopulmonary dysplasia.

Are there any patients in whom red-cell transfusion is beneficial? Clearly, such transfusions can be lifesaving in the setting of acute bleeding, but most transfusions in critically ill patients are not given for acute bleeding. A large body of experimental and clinical evidence suggests that patients with cardiovascular disease do not tolerate anemia well. Among patients who decline to undergo blood transfusion, the odds of death are greater in patients with anemia who have cardiovascular disease than in such patients without cardiovascular disease. But results from observational studies of transfusion in patients with acute coronary syndromes or underlying cardiovascular disease are conflicting.

In addition to death, many other clinically relevant end points — including myocardial infarction, infection, and functional recovery — require evaluation. An ongoing clinical trial, called Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) (chaired by Dr. Carson), will compare an aggressive transfusion strategy with a strategy based on symptoms in patients with cardiovascular disease or other risk factors. Until such patients and those with other conditions are evaluated in clinical trials, uncertainty among clinicians will remain, along with variations in transfusion practice.

Where does this leave us now? Red-cell transfusion has always made sense to physicians when the hemoglobin concentration is low, particularly in a sick patient. The face validity of this idea has driven transfusion practice for much of the past century and frequently still does today. The weight of evidence, however, does not support the unrestricted use of red-cell transfusion in critically ill patients. Instead, a transfusion trigger of 7.0 g per deciliter for most critically ill adults and children appears to be appropriate. A higher threshold might be indicated for patients with cardiovascular disease, pending the completion of further
clinical trials. Red-cell transfusion should no longer be regarded as “may help, will not hurt” but, rather, should be approached as “first, do no harm.”

Dr. Corwin reports receiving grant support and consulting and lecture fees from Ortho Biotech and Johnson & Johnson Pharmaceutical Research Development. Dr. Carson reports receiving grant support from Ortho Biotech. No other potential conflict of interest relevant to this article was reported.

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The Decrease in Breast-Cancer Incidence in 2003 in the United States

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SUMMARY

An initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries shows that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 6.7%) in 2003, as compared with the rate in 2002. Data from 2004 showed a leveling off relative to the 2003 rate, with little additional decrease. Regression analysis showed that the decrease began in mid-2002 and had begun to level off by mid-2003. A comparison of incidence rates in 2001 with those in 2004 (omitting the years in which the incidence was changing) showed that the decrease in annual age-adjusted incidence was 8.6% (95% confidence interval [CI], 6.8 to 10.4). The decrease was evident only in women who were 50 years of age or older and was more evident in cancers that were estrogen-receptor–positive than in those that were estrogen-receptor–negative. The decrease in breast-cancer incidence seems to be temporally related to the first report of the Women’s Health Initiative and the ensuing drop in the use of hormone-replacement therapy among postmenopausal women in the United States. The contributions of other causes to the change in incidence seem less likely to have played a major role but have not been excluded.

Major changes in cancer incidence and death rates, as detected in cancer-registry data, provide unique opportunities to examine questions related to the cause, prevention, detection, and treatment of cancer. In a preliminary report, we suggested that such a major change in breast-cancer incidence occurred in 2003 in the United States.1 In contrast, the 1990s saw an increase in the annual age-adjusted incidence of breast cancer by an average of about 0.5% per year, a rise that was particularly evident among women who were 50 years of age or older2 (Fig. 1). Changes in reproductive factors, in the use of menopausal hormone-replacement therapy, in mammographic screening, in environmental exposures, and in diet have all been proposed to explain the trend. Of these factors, only the use of hormone-replacement therapy changed substantially between 2002 and 2003.

In this report, we provide additional data from 2004 that show little change in breast-cancer incidence between 2003 and 2004. A comparison of incidence rates in 2001 with those in 2004 (omitting the years in which the incidence was in the process of changing) showed that the decrease in annual age-adjusted incidence was 8.6% (95% CI, 6.8 to 10.4).

The decrease in breast-cancer incidence began in mid-2002 and occurred shortly after the highly publicized series of reports from the randomized trial of the Women’s Health Initiative, which reported a significant increase in the risks of coronary heart disease and breast cancer associated with the use of estrogen–progestin combination therapy.3 By the end of 2002, the use of hormone-replacement therapy had decreased by 38% in the United States, with approximately 20 million fewer prescriptions written in 2003 than in 2002.4,5

The analyses we report here used information from the SEER Program of the National Cancer Institute (NCI) collected from nine cancer registries reporting on 9% of the U.S. population. Trends in the incidence of female breast cancer were age-adjusted to the standard population in the year 2000 and were adjusted for reporting delays. Joinpoint (version 3.0) statistical software (http://srab.cancer.gov/joinpoint/) was used for fit-
ting trends over time and to evaluate when changes in trends occurred. The number of patients with unknown estrogen-receptor status changed from 15% in 2001 to 8% in 2004; to adjust for this change, multiple imputation was used to generate estrogen-receptor values for missing data.

Comparison of incidence rates in 2001 with rates in 2004 (omitting the years in which the incidence was rapidly changing) showed that the decrease in annual age-adjusted incidence was evident only in women who were 50 years of age or more. During that period, there was an increase of 1.3% (95% CI, −3.1 to 5.8) in incidence for women below the age of 50 years, a decrease of 11.8% (95% CI, 9.2 to 14.5) for women between the ages of 50 and 69 years, and a decrease of 11.1% (95% CI, 7.9 to 14.2) for women 70 years of age or older.

For women between the ages of 50 and 69 years, the decrease was more evident in those with estrogen-receptor–positive tumors (14.7%; 95% CI, 11.6 to 17.4) than in those with estrogen-receptor–negative tumors (1.7%; 95% CI, −4.6 to 8.0). The decreases were similar for localized disease (11.3%; 95% CI, 8.0 to 14.6) and more advanced disease (13.6%; 95% CI, 9.2 to 17.9) and were evident in primary breast cancers (13.7%; 95% CI, 11.0 to 16.4) but not in contralateral second primary or later breast cancers, for which there was a nonsignificant increase (9.4%; 95% CI, −1.6 to 20.5).

Figure 2A shows the quarterly, age-adjusted incidence rates of breast cancer in women between the ages of 50 and 69 years, categorized according to estrogen-receptor status. The data for change in trend were examined with the use of Joinpoint statistical software. Changes in trend in mid-2002 and mid-2003 were evident for all patients and for patients with estrogen-receptor–positive tumors but not for those with estrogen-receptor–negative tumors. However, the low incidence of estrogen-receptor–negative tumors limited the statistical ability to detect a change in trend. For all patients, the quarterly changes in rate were an increase of 0.08% (95% CI, −0.60 to 0.77) in the first time interval, a decrease of 4.43% (95% CI, −12.66 to 4.75) in the next time interval defined by Joinpoint analysis, and a decrease of 0.04% (95% CI, −1.56 to 1.50) in the last time interval.

What might have been responsible for the sharp decline in breast-cancer incidence, followed by a relative stabilization at a lower incidence rate? One possibility is a SEER reporting flaw, which seems unlikely. The trend for a decrease in incidence in 2003 was evident in all nine SEER registries, there was no statistically significant change in the incidence of cancer other than breast cancer in women during this period, and the lower rates continued in 2004. Could the change have been related to a major decrease in the rate of screening mammography? Although a decrease of 3.2% in this rate was reported for women between the ages of 50 and 65 years for 2003, as compared with that for 2000, such a change would seem insufficient to explain the observation. A change in screening patterns specific to women who formerly received hormone-replacement therapy is also a possibility. For example, if women who discontinued hormone-replacement therapy also stopped receiving mammograms, an apparent decrease in incidence could result. Although visits to physicians would probably decrease among women who discontinued hormone-replacement therapy, no published data are available showing a substantial decrease in mammographic screening in such women. Another possible explanation is that a decrease in incidence is expected in a heavily screened population, similar to that reported for prostate cancer. No sudden decrease has yet been reported for breast-cancer incidence in heavily screened populations.
One of the arguments against changes in mammographic screening as a primary reason for the decline is that the effect was mainly on estrogen-receptor–positive tumors. Breast cancers that are detected on mammography are more likely to be estrogen-receptor–positive than are tumors not detected on mammography (80% vs. 70%), but the difference in the percentages according to estrogen-receptor status is minor. Thus, a drop in screening would result in an approximately equal decrease in estrogen-receptor–positive and estrogen-receptor–negative tumors, an expectation that differed from our findings.

Discontinuation of hormone-replacement therapy could have caused a decreased incidence of breast cancer by direct hormonal effects on the growth of occult breast cancers, a change that would have been expected to affect predominantly estrogen-receptor–positive tumors. If the decrease in breast-cancer incidence had been associated with discontinuation of hormone-replacement therapy, the rapidity of change suggested that clinically occult breast cancers stopped progressing or even regressed soon after discontinuation of the therapy. The hypothesis that hormone withdrawal can rapidly influence the growth of breast cancer is supported by anecdotal reports of regression of breast cancer after discontinuation of hormone-replacement therapy. A cessation of such therapy was associated with a reduction in the proliferative index of breast-cancer cells within 1 month in women with estrogen-receptor–positive tumors but not in those with estrogen-receptor–negative tumors in the same setting, and responses within weeks after estrogen deprivation have been seen in clinical trials of neoadjuvant hormones. An early effect of tamoxifen was seen in the Breast Cancer Prevention Trial, in which the cumulative rates of invasive breast cancer in the tamoxifen group and the placebo group appeared to diverge within the first few months and differed statistically at the end of the first year. An analysis of 51 epidemiologic studies showed that an elevated risk of breast cancer after the use of hormone-replacement therapy had largely if not wholly disappeared within 5 years after discontinuation of therapy, although a more detailed analysis of the time course of changes in risk within this period was not presented.

Notably, the change in the use of hormone-replacement therapy also followed a time course that was similar to the decline in breast-cancer incidence, with a sharp decline followed by a relative stabilization at a new, lower level. The total number of prescriptions for the two most commonly prescribed forms of hormone-replacement therapy in the United States — Premarin and Prempro — had their steepest declines starting in 2002 and particularly in 2003 (62 million pre-

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**Figure 2.** Quarterly Incidence of Breast Cancer in Women between the Ages of 50 and 69 Years, According to Estrogen-Receptor (ER) Status, and the Number of Prescriptions for Hormone-Replacement Therapy (2000–2004).

In Panel A, data are from nine of the NCI’s SEER registries, with trends modeled with regression-analysis statistical software (Joinpoint). Trends were age-adjusted to the standard population in the year 2000 and were adjusted for reporting delays. Panel B shows the number of prescriptions reported in the United States for the combined estrogen–progestin preparation Prempro and the conjugated equine estrogen Premarin, according to year.
scriptions in 2000, 61 million in 2001, 47 million in 2002, 27 million in 2003, 21 million in 2004, and 18 million in 2005)\(^2\) (Fig. 2B). Other medications can influence the incidence of breast cancer. These drugs include tamoxifen and raloxifene, and there is some evidence for beneficial effects of nonsteroidal antiinflammatory drugs, statins, and calcium and vitamin D supplements. However, none of these agents were used by a substantial portion of postmenopausal women or showed substantial change in use during the period from 2000 to 2004.\(^12,13\) Therefore, the drugs are unlikely candidates for causing the decrease in incidence.

When the results of the Women’s Health Initiative hormone trial were announced, women were asked to discontinue their study medications (placebo or hormone) but were encouraged to continue undergoing annual mammography. These women continue to be followed for clinical outcome, and a report of follow-up of the combined estrogen-plus-progesterin trial is anticipated later this year. This report will provide the highest level of evidence concerning the influence of cessation of hormone-replacement therapy on the incidence of breast cancer. Other observers have noted a decline in breast-cancer incidence after 2002. A report from a subgroup of California registries also showed a sharp decrease in breast-cancer incidence in 2003 and suggested that it extended into 2004.\(^14\) A recent analysis of national cancer data by Jemal et al.\(^15\) showed a decline in the incidence of breast cancer in 2003 but did not comment on its clinical relevance. The joinpoint in that study was done with annual (rather than quarterly) data. Annual rates obscure within-year trends, in this case within years 2002 and 2003. In addition, the statistical method used by Jemal et al. cannot select the final year in a range (in this case, 2003) as demonstrating a discontinuity.

It is possible that the ultimate understanding of the effect of cessation of hormone-replacement therapy will be complex; it will probably depend on more than one mechanism and will be affected in different ways by various forms of postmenopausal hormone-replacement therapy. The time course of the decrease in breast-cancer incidence is of both practical and theoretical interest. Our data suggest that much of the decrease in breast-cancer incidence that is attributable to changes in the use of hormone-replacement therapy has already occurred, but important questions remain. Can we expect only a delay in the appearance of clinically detectable tumors, with no reduction in long-term incidence, or will there be a long-term reduction? A change in the hormonal milieu may have slowed the growth of tumors slightly or temporarily. If this is the case, as the use of hormone-replacement therapy stabilizes, breast-cancer incidence should rise again. Alternatively, the change in hormonal milieu may have a more profound effect, similar to that of hormonal adjuvant therapy.\(^16\)

We believe that the data are most consistent with a direct effect of hormone-replacement therapy on preclinical disease, but this conclusion does not rule out some contribution from changes in screening mammography. In any case, attempts to understand the rapid reduction in incidence using theoretical models of breast-cancer evolution and the effects of screening and treatment — such as those of the NCI’s Cancer Intervention and Surveillance Modeling Network\(^17\) — may lead to new insights into the development and prevention of breast cancer.

No potential conflict of interest relevant to this article was reported.

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Ketek — The FDA Perspective

TO THE EDITOR: In response to the article by Ross in this issue of the Journal, we wish to clarify how the Food and Drug Administration (FDA) reviewed Ketek (telithromycin). Although there are other statements or suggestions in the article that also need clarification, we address a few key points in the limited space available here.

First, safety concerns were identified by the FDA early in the review process and taken very seriously throughout four years and three review cycles. The FDA’s approval decision followed a careful review of the safety data submitted, including foreign postmarketing adverse-event reports that accumulated during the FDA’s review of the application. Although the FDA did not rely on study 3014 to support approval, we reviewed the study for safety findings that would have counted “against the drug,” as is consistent with good review practice.

Second, there was no intention to deceive the advisory committee or the public regarding our review of study 3014. Before the second advisory committee meeting, the FDA had only preliminary information regarding inspections of a few of over 1800 clinical study sites. Although the findings at one site had raised serious data-integrity concerns and had led to a referral for criminal investigation, we did not know at that time that we would conclude months later, after additional inspections and further review, that the entire study should not be relied upon. The FDA did not discuss data-integrity issues at the second advisory committee meeting to avoid compromising the ongoing investigations, recognizing that the FDA retained the ultimate decision authority.

Finally, noninferiority studies were considered acceptable as the basis for approval for treatment of certain respiratory infections when the Ketek New Drug Application was submitted. Concurrent with the Ketek review, our thinking on noninferiority studies was evolving. Today, noninferiority studies are no longer considered acceptable for two of the three indications for which Ketek was originally approved. We are applying this new regulatory position to more recently submitted and planned applications.

The FDA monitored the safety of Ketek after approval and conducted a 1-year postapproval safety review in the spring of 2005. After three reports of serious hepatotoxicity were published in January 2006, we conducted an analysis of the available safety data that led to the addition of a bolded warning regarding hepatotoxicity in June 2006. After an advisory committee review of Ketek in December 2006, in February 2007 we added a boxed warning and Medication Guide to the label and removed two indications. Although we believe
that the potential benefits of Ketek outweigh its risks when it is used according to the current approved label, we continue our safety surveillance and will take further actions if warranted.

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To the Editor: Schade et al. (Jan. 4 issue)\(^1\) report an adjusted incidence-rate ratio of 4.9 for valvular regurgitation among patients taking the dopamine agonist cabergoline, especially at a daily dose above 3 mg and a duration of use of 6 months or more. The authors also report an incidence-rate ratio of 2.6 for cabergoline at a dose of 3 mg or less, adjusted for the cumulative duration of use. In the same issue, Zanettini et al.\(^2\) report a relative risk of moderate or severe valvular regurgitation of 4.6 to 7.3 among patients taking cabergoline. They also describe a dose effect on the severity of valvular dysfunction. Of note, Zanettini et al. do not report the prevalence of left ventricular dilatation and remodeling, which weakens their assertion that the tenting area of the mitral valve is solely an index of “stiffening of the leaflets.”

Cabergoline is a first-line therapy in prolactin-secreting pituitary tumors. The usual dose is 0.25 to 2.0 mg weekly (maximum, 4.5 mg). Young patients with hyperprolactinemia often receive therapy for life. Have the authors examined the prevalence of valvular dysfunction at lower doses of cabergoline in their studies? Further work with rigorous quantitative echocardiography is required to study the effect of lower doses of cabergoline administered over a long period in patients with hyperprolactinemia.

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TO THE EDITOR: Schade et al. and Zanettini et al. report that the ergot-derivated dopamine agonists pergolide and cabergoline are associated with a significant risk of heart-valve regurgitation, a risk not associated with dopamine agonists that are not derived from ergot. In these articles and the accompanying Perspective article by Roth, the suggested explanation for this difference is mitogenesis caused by ergot-derivated products binding to serotonin (5-hydroxytryptamine [5-HT]) receptor subtype 5-HT$_{2B}$. Roth notes that other 5-HT$_{2B}$ agonists, such as fenfluramine, ergotamine, and methysergide, can also cause valvular heart disease.

Methysergide is a well-known cause of retroperitoneal fibrosis. Agonists at 5-HT receptors have been associated not only with hyperplasia in cardiac valves but also with liver fibrosis. These observations suggest that retroperitoneal fibrosis that is associated with methysergide and possibly with other drugs may be due to agonism at 5-HT receptors.

Furthermore, atypical antipsychotic medications, such as risperidone and ziprasidone, are potent 5-HT–receptor antagonists. If a medication that is a 5-HT$_{2B}$ agonist must be used, then an atypical antipsychotic agent might be started as well to provide prophylaxis against mitogenic effects.

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TO THE EDITOR: The Perspective article by Roth brings to mind endomyocardial fibrosis, a restrictive cardiomyopathy linked to carcinoid and hypereosinophilic syndromes. Originally described by Davies in Uganda, endomyocardial fibrosis is endemic in sub-Saharan Africa and is characterized by thickening of the valve leaflets and fibrosis of the outflow tracts that progress to regurgitant heart failure. Endomyocardial fibrosis is linked to poverty and eosinophilia, but its cause is unknown.

Is there a link between endomyocardial fibrosis and the 5-HT$_{2B}$ receptor? Agonists of 5-HT$_{2B}$ do not universally cause valvulopathy, and a dose response is evident. Genetic polymorphisms in receptor genes may influence receptor activation and downstream pathological responses. Dietary exposure to 5-HT$_{2B}$ agonists might be implicated in endomyocardial fibrosis in Africa. Serotonin interacts with eotaxin to promote eosinophilia.

Thus, we are curious whether any of the affected patients described by Schade et al. and Zanettini et al. had eosinophilia, as compared with controls. If 5-HT$_{2B}$ is an important etiologic factor in the development of endomyocardial fibrosis, an interaction among 5-HT$_{2B}$ polymorphisms, eosinophilia, and environmental exposure (e.g., dietary tryptophan) could be explored.

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TO THE EDITOR: Schade et al. and Zanettini et al. report a causal association between 5-HT$_{2B}$ agonism and valvular heart disease. The accompanying commentary by Roth suggests that the valvulopathy could be due to valve-cell overgrowth stimulated by 5-HT$_{2B}$–receptor agonists. Valvular remodeling has also been ascribed to an embryonic proliferative expansion process, based on transdifferentiation of precursors to a myofibroblast-like phenotype.

Along these lines, we suggest a mechanism that may involve recruitment and differentiation of circulating or cardiac stem cells induced by 5-HT$_{2B}$–receptor activation. Our recent unpublished data from studies of embryonic stem cells show a role of 5-HT$_{2B}$ receptors in cardiac differentiation. Myocytes derived from embryonic stem cells express 5-HT$_{2B}$ receptors during development (Fig. 1). Serotonin stimulation promotes cell differentiation through a process sensitive to selective 5-HT$_{2B}$–
Dr. Schade and colleagues reply: Stephens et al. and Linkova et al. focus on the potential association of low-dose pergolide or cabergoline therapy with valvular heart disease. In our study, the incidence-rate ratio for newly diagnosed cardiac-valve regurgitation was 5.1 (95% confidence interval [CI], 1.3 to 20.4) with 3 mg or less of pergolide and 2.6 (95% CI, 0.5 to 12.8) with 3 mg or less of cabergoline. Further stratification (e.g., for doses of 1 mg or less) was not possible because of the small number of exposed patients. Systematic echocardiographic studies are required to investigate the effect of treatment with low-dose pergolide or cabergoline over a period of several years.

Ziegler and Bukhman discuss the potential role of eosinophilia in endemic endomyocardial fibrosis in Uganda. In our study, none of the patients with newly diagnosed heart-valve regurgitation had a recorded finding of eosinophilia during the study period.

Kast and Altschuler suggest that mitogenic effects of 5-HT\(_{2B}\) agonists may be antagonized by atypical antipsychotic agents such as risperidone and ziprasidone. From the pharmacologic point of view, this is an interesting hypothesis. However, treatment with atypical antipsychotic agents may cause additional adverse reactions. Antipsychotic agents such as risperidone and ziprasidone may interfere with the efficacy of dopaminergic treatment and may aggravate parkinsonism. In addition, there is a concern that atypical antipsychotic agents are associated with an increased risk of death in elderly patients with dementia. Thus, routine coadministration of atypical antipsychotic agents seems to be problematic from the clinical point of view, especially considering the availability of dopamine agonists without 5-HT\(_{2B}\) agonism (e.g., non–ergot-derived dopamine agonists or ergot-derived lisuride, which is a potent 5-HT\(_{2B}\) antagonist\(^2\)).

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DRS. ZANETTINI AND PEZZOLI REPLY: In response to the question about endomyocardial fibrosis posed by Ziegler and Bukhman: we have the complete blood counts of approximately 80% of our patients for the past 12 months and have not seen any cases of eosinophilia. Our nutritionist reports that their diet was low in tryptophan. Since tryptophan is a

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**Figure 1. Expression of 5-HT\(_{2B}\) in Murine Embryonic Stem Cells and Differentiating Embryoid Bodies.**

Reverse-transcriptase polymerase chain reaction was used to amplified messenger RNA (mRNA) for 5-HT\(_{2B}\) from samples of mRNA obtained from murine embryonic stem cells (ESC) and from embryoid bodies at 4, 8, and 12 days of differentiation (EB4, EB8, and EB12, respectively). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA amplification was used as a control for the quantity of mRNA.

2. Sutherland FW, Perry TE, Yu Y, et al. From stem cells to adult stem cells. Since adult stem cells can differentiate into valvular interstitial cells, one could speculate that 5-HT\(_{2B}\) receptors are implicated in this process.
neutral, large amino acid that competes with levodopa for absorption, patients with Parkinson’s disease are told to avoid tryptophan-rich foods.

The proposal by Kast and Altschuler to use risperidone or ziprasidone as an atypical antipsychotic agent and 5-HT-receptor antagonist in patients with Parkinson’s disease is theoretically correct. However, in clinical practice, the antiparkinomegic effects of these drugs are fairly powerful, and they have a major negative effect on motor function, which would prevent us from using them routinely.

The data cited by Linkova et al. are consistent with ours, since the subgroup of our patients who were exposed to a mean cumulative dose of pergolide of 4566 mg (close to the cumulative dose of 4541 mg that they cite) did not have moderate-to-severe regurgitation. However, Linkova et al. did record discrete leaflet thickening in 11.1% of their patients, as compared with none in healthy volunteers. The phenomenon appears to depend on the cumulative dose, but we are unable to set a safety threshold.

The hypothesis that the mitral tenting area could be used as an early marker of leaflet stiffness is based mainly on the finding that the area was significantly greater in the ergot group without valvular disorders (grade 0 or 1) than in controls (2.68 vs. 2.37 cm², P = 0.02).

To exclude the possibility that left ventricular remodeling influenced this measure in patients with intermediate-grade regurgitation, we compared left ventricular end-diastolic volume, adjusted for body-surface area, in patients with grade 0 to grade 2 regurgitation who were receiving ergot with that in patients with grade 3 regurgitation of the mitral or aortic valve, and we did not find a significant difference (54.9±10.6 ml per square meter vs. 55.3±13.0 ml per square meter among patients with grade 3 regurgitation, P = 0.003).

We have no data on low-dose cabergoline, since we do not follow patients with prolactinomas. This is a worthwhile area of investigation.

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**DR. ROTH REPLIES:** Kast and Altschuler propose the intriguing hypothesis that since methysergide, which is a prodrug for the potent 5-HT₂a agonist methylergonovine, is associated with retropitoneal fibrosis, the cause of this condition may be 5-HT₂a agonism. This is an interesting idea, and there have been many case reports and other studies linking the use of pergolide with an increased incidence of retropitoneal fibrosis, although we await definitive evidence. Kast and Altschuler also suggest that certain atypical antipsychotic drugs such as risperidone and ziprasidone might be used for prophylaxis in the rare circumstance when a drug with 5-HT₂a agonism cannot be avoided. (Risperidone and ziprasidone have Kᵢ values of 41.5 nM and 27 nM, respectively, according to the Psychoactive Drug Screening Program’s Kᵢ database, available at http://pdsp.med.unc.edu/pdsp.php.) The absolute affinities of these drugs are rather low, and atypical antipsychotic drugs are costly medications with a large number of potentially serious side effects. Instead, I would recommend cyproheptadine, which is a generic, high-affinity 5-HT₄ antagonist with a Kᵢ value of 1.4 nM, according to the above-mentioned database.

Ziegler and Bukhman wonder whether there might be some association among various 5-HT₂b–receptor polymorphisms, eosinophilia, dietary tryptophan, and endomyocardial fibrosis. This is another interesting idea worthy of further study.

Sartiani et al. suggest an interesting model in which cardiac stem cells might be recruited through 5-HT₂b activation. After recruitment, further 5-HT₂b stimulation presumably would induce overgrowth and fibrosis. My colleagues and I have previously reported that 5-HT₂b–receptor activation induces mitogenesis in human cardiac-valve interstitial cells in vitro, so there is merit to the idea that 5-HT₂b–receptor activation may induce mitogenesis of cardiac-valve cells. Sartiani et al. also show that what appears to be 5-HT₂b–receptor mRNA is present in embryonic stem cells, but they do not provide evidence of functioning 5-HT₂b receptors in these cells. Although their hypothesis is intriguing, it will be important to demonstrate the presence of functional 5-HT₂b receptors, since we have frequently found that the presence of receptor mRNA does not always indicate functional receptor protein.

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TO THE EDITOR: Imboden et al. (Dec. 28 issue) report preferential transmission of mutant alleles in the KCNQ1 gene (11p15.5) from mothers to daughters and propose that these mutations confer a selective reproductive advantage. However, allele-specific transmission-ratio distortion and grandparental-origin–dependent transmission-ratio distortion have been described previously for 11p15.5. Specifically, the 11p15.5 alleles of a maternal grandmother are more likely (61%) to be transmitted to her granddaughters than to her grandsons. The transmission of 11p15.5 alleles that is dependent on their grandparental origin is consistent with these observations. Indeed, if females are more likely to be affected, the mutant KCNQ1 alleles may be more likely to have originated with the grandmother in these families. The observed bias in their transmission may be associated with the grandparental origin of the alleles rather than with the reproductive advantage of the mutations. I would predict, therefore, that in families in which the mutation has been inherited from the maternal grandmother, preferential transmission would be detected, whereas in families in which the mutation originated in the grandfather, transmission to female offspring would be less likely.

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THE AUTHORS REPLY: Naumova and her colleagues previously reported transmission distortion for imprinted chromosomal regions including the locus for the long-QT syndrome type 1, 11p15.5. They suggested that imprinting defects and selective embryonic loss could lead to the skewed transmission and that 11p15.5 alleles were transmitted preferentially from grandmothers to granddaughters. However, they also reported a favored transmission of alleles from maternal grandfathers and paternal grandmothers to grandsons.

We have reported that the increased transmission of long-QT syndrome types 1 and 2 from mothers to daughters contributes to the female predominance in this disease, and we have suggested a positive selection of mutation carriers in general. Although parent-of-origin methylation patterns might be involved in the transmission distortion observed at the locus for long-QT syndrome type 1, it is not clear how the selective loss of embryos might relate to preferential transmission of the mutated long-QT syndrome type 1 allele from mothers to their offspring. Differences in the transmission ratios between long-QT syndrome types 1 and 2 that are specific to the sex of the offspring suggest that more than one mechanism might lead to transmission distortion. In addition, the long-QT syndrome type 2 locus (7q35-q36) is not known to be imprinted. Further studies investigating mechanisms of non-mendelian transmission in human disease and embryonic development are certainly needed.

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Persistent Coronary Occlusion after Myocardial Infarction

TO THE EDITOR: The Occluded Artery Trial (OAT), reported by Hochman et al. (Dec. 7 issue), compared percutaneous coronary intervention (PCI) with stent placement and optimal medical therapy with optimal medical therapy alone in patients who had persistent coronary occlusion after myocardial infarction. This report and the group’s earlier report on the trial design indicate that the study was designed to have 90% power to detect a 25% reduction in the rate of the primary end-point event—a composite of death, myocardial infarction, or New York Heart Association (NYHA) class IV heart failure—in patients undergoing PCI, assuming a 3-year event rate of 25% with medical therapy. The number of observed events required to meet these characteristics is nearly 508. The report includes only 301 study events (approximately 60% of the expected rate), suggesting that the report was published well before full information was available.

A data and safety monitoring board oversaw the conduct of the trial and performed interim monitoring. The study may have been published before full information was available because the board recognized that a futility analysis showed that the estimated hazard ratio in the PCI group (1.16) was inconsistent with the alternative hypothesis (hazard ratio, 0.75) (P<0.001). Thus, it was nearly certain that the study would never show a benefit of PCI. If this is indeed what happened, it should have been disclosed in the report.

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TO THE EDITOR: Hochman et al. found no clinical evidence to support the open-artery hypothesis. However, OAT failed to enroll the ideal patient in whom to test this hypothesis. In studies in animals, late reperfusion has been shown to limit the degree of infarct expansion in a nonsalvageable infarct zone. In sharp contrast, the majority of patients (>85%) in this trial had collateral vessels at baseline, a finding presumably responsible for the high prevalence of viability of the infarct zone (69% of patients in the viability substudy). Arguably, delayed recanalization of the infarct-related artery in this setting will lead to loss of previously recruited collateral flow, reexposing the once-protected distal vascular bed and viable

myocardium to future upstream vascular events. The inclusion of patients without existing collateral vessels might have provided a more appropriate clinical model to test the late open-artery hypothesis. No analysis of the subgroup of patients without collateral vessels was reported, although such an analysis would be of great interest.

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TO THE EDITOR: Hochman et al. report that there was no significant difference in mortality between the PCI group and the medical-therapy group. Rates of mortality due to arrhythmia were not reported, although a substantial number of patients in each group might have died from ventricular arrhythmia. Nothing was said about the number of patients who received an implantable cardioverter–defibrillator (ICD) or cardiac resynchronization therapy during follow-up. Both these interventions reduce the total mortality and mortality due to arrhythmia among survivors of myocardial infarction with ejection fractions of less than 35%.1,2 If there was a significant difference between the two study groups in rates of use of ICDs and cardiac resynchronization therapy, it might have affected the mortality rates and the result of the study. In contrast, a similar rate in the two groups might have obscured the potential benefit of restoring antegrade flow in the occluded infarct-related artery for reducing the risk of death from arrhythmia.

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TO THE EDITOR: In their editorial accompanying the report on OAT, Hillis and Lange suggest that the use of beta-blockers in the study may have obscured the benefits of restoring antegrade flow after myocardial infarction, and that all survivors of myocardial infarction should receive a beta-blocker indefinitely. Although beta-blockade has been shown to be beneficial in high-risk patients, such as those with heart failure, ischemic symptoms, arrhythmias, or persistent occlusion, the benefit of long-term beta-blocker therapy in an unselected population of patients after myocardial infarction is less clear.3 The majority of trials of long-term beta-blocker therapy after myocardial infarction were conducted in the era before routine use of aspirin, statins, thrombolysis, and angiotensin-converting–enzyme inhibitors; did not include large numbers of patients; and showed a long-term mortality benefit only when the results of individual trials were pooled.2,3 Although long-term use of beta-blockers after myocardial infarction is strongly encouraged in current guidelines
and is commonly practiced, the true benefit of beta-blockers with current medical therapy in an unselected patient population remains unclear.

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THE AUTHORS REPLY: De Luca and Tomai ask about the quality of life of patients in OAT. We found only a transient reduction in angina with PCI; by 3 years, there was no significant difference between the PCI group and the medical therapy group in the prevalence of angina (9.1% and 10.3%, respectively; P = 0.53). Moreover, PCI is appropriately used for the treatment of angina refractory to optimal medical therapy. Data on quality of life and economic data were collected for a subgroup of patients but have not yet been reported. There was no suggestion that PCI reduced the rates of death, myocardial infarction, or heart failure in subgroups with indicators of high risk (e.g., anterior infarct and low ejection fraction).

With regard to Anderson’s concerns, our study was not an event-driven trial, and the data and safety monitoring board did not stop the trial because of futility. The observed rate of heart failure was lower than projected, accounting for the lower-than-expected number of events. The trial did, however, achieve 81% power to detect the targeted relative risk reduction at an alpha level of 0.05 and the observed event rates.

Erdogan brings up a valid point about the potential for confounding on the basis of the patients’ status with respect to ICD and cardiac resynchronization therapy. In the PCI group, 2.4% of the patients received an ICD, and in the medical therapy group, 1.8% received an ICD — a difference that was not significant. Data on cardiac resynchronization therapy were not collected; however, most cardiac resynchronization devices have the function of an ICD, which would have been captured in our ICD data. It is unlikely that the rate of cardiac resynchronization therapy would have differed significantly between the two randomized study groups, since there were similar event rates over time for all measures of heart failure.

The comments of Nagajothi and colleagues provide an interesting contrast to the comments of Wong. Nagajothi and colleagues suggest that PCI may be more beneficial in patients with inducible ischemia, and Wong suggests that PCI may be beneficial only when there is no viability in the infarct zone. There was no interaction between either the presence of collaterals or ischemia on stress testing and the treatment effect in our trial.

In their editorial, Hillis and Lange note that they have shown an association between beta-blockers and improved survival among patients with persistent occlusion of the infarct-related artery and suggest that PCI might have had an effect on events in patients in OAT who were not receiving beta-blockers. A total of 263 patients in the trial were not given beta-blockers at discharge, whereas 1886 patients were. The primary end point did not differ significantly according to the study treatment in either of these two subgroups. The cumulative 4-year event rate for the death, reinfarction, and class IV heart failure was 17.0% in the PCI group and 17.9% in the medical therapy group among patients who were not given beta-blockers at discharge, whereas 1886 patients were. There was no interaction between treatment and the prescription of beta-blockers at discharge for the primary end point (P = 0.40).

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for the Occluded Artery Trial Investigators

**The Editorialists Reply:** Several placebo-controlled trials, encompassing data from more than 35,000 survivors of acute myocardial infarction who did not receive reperfusion therapy, have shown that long-term therapy with beta-adrenergic blockers (propranolol, timolol, and metoprolol) reduces long-term mortality. As noted by Chua et al., this salutary effect is greatest in so-called high-risk patients — those of advanced age or with evidence of large infarction, anterior infarction, complex ventricular ectopy, or hemodynamic evidence of left ventricular systolic dysfunction. Even for survivors of myocardial infarction who are not at high risk, however, long-term beta-blocker therapy is recommended, unless, of course, a contraindication is present.

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**Antibiotic Prophylaxis in Colorectal Surgery**

**To the Editor:** Fifteen years ago, Martin et al. showed that when a single intravenous dose of 2 g of cefotetan was administered to patients immediately before colorectal surgery, adequate concentrations of cefotetan in both the blood and colonic wall were maintained during surgical anastomosis (for a mean ±SD period of 151±54 minutes) and throughout surgery. These concentrations of cefotetan remained superior to the minimum inhibitory concentrations of the drug for 90% of *Staphylococcus aureus* (16.0 mg per liter), *Escherichia coli* (0.05 mg per liter), and *Bacteroides fragilis* (8.0 mg per liter). However, concentrations of cefotetan in the abdominal wall and epiploic fat were no longer sufficient to provide protection against *S. aureus* and *B. fragilis* on surgical closure (216±76 minutes). Thus, Martin and colleagues suggested an additional dose of 1 g of cefotetan before closure to achieve adequate protection.

In the study by Itani and colleagues (Dec. 21 issue), low concentrations of cefotetan at closure due to inappropriate timing of preoperative antibiotic administration (60 to 119 minutes before incision in many patients), prolonged surgery (up to 313 minutes), and obesity (in 27% of the patients for whom doses were not adjusted), as well as increased minimum inhibitory concentrations of cefotetan may have contributed to the differences between the study groups in the incidence of superficial incisional infection and cefotetan failure.

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To the Editor: The incidence of postoperative infection in the study reported by Itani and colleagues was extraordinarily high. The search for a new antibiotic to reduce this rate of infection not only does not bring the rate of infection into an acceptable range but also ignores a critical cause of surgical-site infection—the surgical technique. In the prevention of wound infections, more antimicrobial agents for use as prophylaxis will never overcome errors in surgical technique.

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The Authors Reply: Moine and Asehnoune note that the timing of the administration of antimicrobial agents, the dose, and the possible need for additional administration are important factors in the success of prophylaxis against surgical-site infection. The longer half-life of ertapenem, as compared with that of cefotetan, permits simpler dosing in longer procedures and in patients in whom the 60-minute window of administration is missed. In our analysis, a lower body-mass index, the use of ertapenem, and a shorter duration of surgery were independent predictors of a better outcome, but the timing of prophylaxis was not.

Spievack points out that surgical technique is another important factor in the prevention of surgical-site infection. In our prospective study, patients were randomly assigned to receive either ertapenem or cefotetan and were operated on by the same groups of surgeons in 51 institutions. The rate of surgical-site infection in this study was similar to that in other studies in which the proper definition of surgical-site infection and follow-up were instituted. This high rate of surgical-site infection reflects a problem in elective colorectal surgery that surgeons need to acknowledge and address. Although more antibiotics are not the solution, better antibiotics can help.

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International Aeromedical Evacuation

To the Editor: In their review of international aeromedical evacuation, Teichman and colleagues (Jan. 18 issue) mention that infectious diseases are contraindications to aeromedical evacuation. In fact, because of the strict criteria on suitability for air transport of patients who have infectious diseases, even those with severe acute respiratory syndrome (SARS), the benefits of air transport clearly exceed the risk. During the SARS outbreak in Asia, patients with suspected SARS were safely transported by air with the use of an airtight portable isolation unit. Negative-pressure portable isolation units are equipped with air-purifying respirators. The construction is light and durable and has working ports through which the medical crew can monitor patients and perform procedures. So far, four patients with active pulmonary tuberculosis have also been safely transported in such novel isolation units, with an average flight time of 8 hours. The medical crews reported no problems during or after transport (unpublished data). Meticulous preparation for air transport and posttransport monitoring are mandatory for transporting patients with communicable diseases who require respiratory isolation.

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To the Editor: Teichman et al. do not discuss the significant financial gains that air-ambulance
companies and local “expat clinics” serving them derive from evacuations. Such gains may lead to evacuations even when satisfactory local care is available. We have seen air evacuations of patients with uncomplicated dengue fever, with discharge of the patients the next day. A tourist who was evacuated by air ambulance to Bangkok because of “exfoliative dermatitis” was found instead to have a drug-related maculopapular rash. Evacuation companies and their “expat clinics” tend to downgrade local health care capabilities instead of seeking out capable local doctors with language and communication skills and developing cooperative care. This increases costs and hinders improvements of local facilities. Moreover, eagerness to evacuate can result in delay of urgent care.1

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TO THE EDITOR: Teichman and colleagues present a comprehensive guide to evacuation for medical emergencies in travelers. I recently volunteered at an AIDS clinic in East Africa and was asked to help evaluate and care for a Canadian missionary in whom an unstable cardiac arrhythmia had developed. Even though we were in a city with a regional referral hospital, the intensive care unit had few intravenous medications and no defibrillator. We decided to have the patient flown by air ambulance to Nairobi. Fortunately, he had purchased evacuation insurance and remained in stable condition during the 18 hours it took to get approval from the insurance company’s medical director and then to wait for daylight so that the plane could land.

The situation led to discussions among the expatriate doctors and researchers and the native medical officers and students about the blatant difference between the standard of care expected by travelers and that received by the natives dying (without even intravenous fluids or antibiotics) in the medical wards just next door. What about the ethics of international evacuation?

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THE AUTHORS REPLY: We agree with Tsai et al. that as advanced equipment becomes available and reliable treatment protocols are developed, fewer medical conditions will be contraindicated aboard aircraft. However, portable isolation units used during domestic transfers may not effectively accommodate patients undergoing international aeromedical evacuations lasting longer than 2 to 4 hours.1 Nor are these units likely to assuage concern about transporting patients who are harboring infectious diseases that have pandemic potential. Highly infectious diseases merit consideration that extends beyond individual patient or provider preferences and capabilities. During the 2003 SARS outbreak and aircraft-borne transoceanic spread, international aeromedical evacuations were sharply curtailed, governments prohibited entry to infected travelers, and hospitals refused admission of suspect patients.2 Similar “social distancing measures” that are likely to ground aircraft have been incorporated into global containment operations, should epidemiologic signals indicate an approaching pandemic.3

Wilde’s assertion that financial gains were not discussed neglects our statements that “Financial considerations alter the transfer process when economic incentives become entangled with patient advocacy,” and that “an evacuation represents a substantial financial gain to the company that completes the transfer.” Nevertheless, we share his concern regarding the intrusion of economic triage into clinical decision making and recognize that no medical specialty or setting is immune to its distorting effects. For those who make decisions about international transfer, we hope our review offers rational guidance.

We are not aware of support for the concept that “expat clinics” downgrade local health care capabilities or hinder opportunities for improving local facilities. International health clinics are inclusive enterprises that care for a wide variety of patients (“local” patients account for more than 70% of the patient base at one author’s health center). International doctors who live in developing nations can provide high-quality care to all patients, train their colleagues in effective practices, and encourage their colleagues to remain in their home countries, rather than entice them to migrate to wealthier nations. Hence, international physicians are part of the solution to reducing global health disparities.
Brown is troubled by differences in the medical care received by wealthy travelers and that received by impoverished native citizens. Using the benefits of personal contingency planning for an injured or ill person presents less of an ethical dilemma than nationalized responses to incidents of mass disaster where “en masse scoop and run” of foreign nationals occurs against a backdrop of “sheltering in place” of local residents who are often more seriously injured. A noble strain of ignoring the boundaries of politics, race, and economics in order to provide care runs through the history of medicine. Embracing it could be the first step to erasing the blatant differences that Brown decries.

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Recombinant PTH for Initial Management of Neonatal Hypocalcemia

TO THE EDITOR: Neonatal hypocalcemia due to hypoparathyroidism can present as life-threatening seizures or tetany. Currently, initial management consists of the administration of calcitriol and high doses of calcium. In symptomatic children, to avoid extravasation, intravenous calcium is best administered through a central line, a procedure that requires proper expertise. However, central access carries the risks of infection and thrombosis. Correction of hypocalcemia with intravenous and oral calcium often takes a day or longer to achieve, leaving the infant at risk for seizures and tetany. Therefore, recombinant parathyroid hormone (teriparatide) should be a faster, safer, and more physiologic means of correcting hypocalcemia due to hypoparathyroidism.

A 17-day-old Hispanic boy was taken to an outlying emergency room with generalized seizure and profound hypocalcemia. A review of his history showed that he had had muscle twitches since the second day of life. The workup for sepsis, which included lumbar puncture, was negative. He was transferred to Children’s Hospital in San Diego, having already received a few intravenous boluses of calcium. A nadir calcium level of 4.9 mg per deciliter (with normal albumin) was associated with an elevated phosphorus level (10.1 mg per deciliter), a low magnesium level (1.6 mg per deciliter), and a normal alkaline phosphatase level (178 U per liter [normal range, 110 to 300 U per liter]). Since the results of laboratory studies suggested hypoparathyroidism or pseudohypoparathyroidism, calcitriol was added, with a first dose of 0.5 µg, followed by 0.25 µg per day. The child was no longer having seizures, so a central line was not placed. Despite the administration of oral calcium glubionate every 4 hours and continuous peripheral infusion of diluted calcium gluconate (105 mg of elemental calcium per kilogram of body weight per day), his calcium level rose from 6.2 mg per deciliter to only 6.9 mg per deciliter one day after the addition of calcitriol. When teriparatide became available the next day, he received 5 µg subcutaneously, and his calcium level rose from 6.9 mg per deciliter to 9.3 mg per deciliter in less
than 4 hours. Hypoparathyroidism was subsequently confirmed by test results showing an inappropriately low intact parathyroid hormone level (41 pg per milliliter), with a calcium level of 4.9 mg per deciliter and a normal magnesium level after supplementation (2.2 mg per deciliter). The results were negative on fluorescence in situ hybridization for the DiGeorge syndrome and 46XY karyotype. The child is currently being evaluated for a calcium-sensor–activating mutation, although there is no family history of the disease. His initial ratio of urinary calcium to creatinine of 0.12 could have reflected the mildly low 25-hydroxyvitamin D level (17 ng per milliliter) due to mild maternal vitamin D deficiency.

Although teriparatide has been available to treat osteoporosis in adults, its use in pediatrics has been hampered by concern about long-term exposure and the risk of osteosarcoma. This case demonstrates that after obtaining the diagnostic samples, short-term use of teriparatide can raise calcium levels faster and more safely than can other commonly used methods. This approach may represent an advance in the management of hypocalcemia, particularly in infancy, and should be further evaluated.

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**BOOK REVIEWS**

**PSYCHOSOMATIC MEDICINE**


Lord Chesterfield (1694–1773) wrote, “I find, by experience, that the mind and the body are more than married, for they are most intimately united; and when one suffers, the other sympathizes.” The dilemma of the body–mind connection has perplexed scientists for centuries. Evidence of interest can be found in the earliest writings on the history of medicine. Psychosomatic medicine emerged as the field that focuses on coexisting medical and psychiatric conditions and serves as the interface between the two fields. In June 2005, the first subspecialty examination in psychosomatic medicine was administered by the American Board of Psychiatry and Neurology. The publication of *Psychosomatic Medicine*, edited by Michael Blumenfield and James J. Strain — two distinguished psychiatrists and icons in the field of psychosomatic medicine — closely followed this landmark event.

The book focuses on the challenges of diagnosis and treatment in psychosomatic medicine. Most methods currently used in the field were originally designed for use in pure psychiatric populations, not for patients with coexisting medical conditions. Ignoring the effects of coexisting conditions can result in inaccurate diagnoses and inappropriate treatment. There are numerous examples of disorders that were classified as “psychiatric” by default because their underlying mechanisms were not yet understood; later, scientific discoveries identified physiological mechanisms, and more specific microdiagnoses were assigned. The not-too-distant case of *Helicobacter pylori* is an obvious example. Other intriguing examples that are discussed in this book and that may be reassessed in the future are fibromyalgia, chronic fatigue syndrome, and hyperacusis.

The interaction between psychosocial disorders and cardiovascular disease is another interesting topic. The chapter in *Psychosomatic Medicine* that covers cardiovascular disease begins with the fascinating story of President Dwight D. Eisenhower, who had a myocardial infarction in 1955. His only obvious risk factors then were his type A personality and the overwhelming stress he was under as president. The chapter goes on to discuss the recognition, implications, and treatment of psychosocial risk factors in cardiovascular disease. In addition, it discusses the effects of depression on platelet, endothelial, autonomic, and hormonal functions, as well as other mechanisms that may further complicate cardiovascular disease.

This 51-chapter book is divided into 5 sections: “Evolution of Psychosomatic Medicine,” “Physical Conditions,” “Psychiatric Conditions,” “Special Topics,” and “Future Perspectives.” The first section starts with a chapter on the history of psychosomatic medicine, tracing the specialty from its roots in the early writings of Johann Christian Heinroth in the 19th century to its establishment as a psychiatric subspecialty in 2005. The book contains a wealth of updated information and covers a wide spectrum of frequently encountered clinical problems. It also provides detailed discussions of ethics, forensic applications, pregnancy, sexuality, alcoholism, death and dying, and pain and palliative care. Overall, the chapters are well organized and include sections on diagnosis and treatment. At the end of each chapter, the authors discuss case-based examples of common problems. The book also comes with a DVD that contains the full text and searchable references and that provides users with PowerPoint lectures on selected topics and significant questions and answers that can be used for teaching purposes.

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Understanding Autism: From Basic Neuroscience to Treatment

Autism is an elusive developmental disorder that has been the focus of increasingly intense scrutiny over the past two decades. As with most aspects of research, the more we understand this enigma, the more we realize we have yet to learn. This collection of reviews, written by a who’s who in autism research, eloquently brings the reader up to date on the progress in all pertinent aspects of the research and presents an effective framework for future investigations.

Even for those who work daily in autism research, specialization makes it difficult to keep abreast of the progress in all areas of the field. This book provides outstanding updates in diagnosis, epidemiology, genetics and genomics, neuroanatomy, neurophysiology, neuropsychology, and the neural systems underlying the inherent behavioral aspects of autism. For those unfamiliar with autism, the book contains concise reviews of the myriad facets of the disorder; these reviews are highly appropriate teaching tools for the next generation of clinicians and researchers. Parents, however, may find the book too technical; it is probably not suitable for the average lay reader.

Several chapters merit specific mention. Chapter 9, “Language in Autism,” is a coherent account of the linguistic components that underlie the verbal and nonverbal communication deficits found universally in people with autism. This chapter also includes clear descriptions of the integrative theories of language, including the theory of mind and the procedural memory system. Chapter 17, “Neuropsychology and Neurophysiology of Autism Spectrum Disorders,” is a succinct review of models of cognitive dysfunction in autism, including complex information processing, local–global processing, and executive function. Chapter 19, “Behavioral, Educational, and Developmental Treatments for Autism,” concisely covers appropriate language and social interventions for younger as well as older children with autism, including reviews of comprehensive treatment approaches for preschoolers. Perhaps the most powerful chapter is the final one, “The Costs of Autism,” an articulate outline of the exorbitant direct and indirect costs of autism to the individual, to families, and to society in the 21st century.

This book is somewhat difficult to read from cover to cover because it lacks a common thread to connect the chapters. Although described in the preface as comprising six distinct sections (diagnosis and epidemiology; genetics and genomics; behavior and underlying neural systems; clinical findings in neuropsychology, neuroanatomy, neuroimaging, and neurophysiology; treatment; and economics), the book contains no section introductions and no text to link the topics between and across sections and chapters. The section on neural systems and behavior (chapters 7 through 13) is especially disjointed, with the chapter topics jumping from fear and anxiety to cerebellar networks to language, the prefrontal cortex, the amygdala, and the thalamus. These drawbacks notwithstanding, this book is a seminal work that makes a highly important contribution to the field of autism research.

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Autism: A Neurological Disorder of Early Brain Development

There is a bit of irony that not since the time of Bruno Bettelheim’s The Empty Fortress: Infantile Autism and the Birth of the Self (New York: Free Press, 1967) has autism enjoyed so much interest. There has been an explosion of research into the causes of and treatments for autism (both rational and not so rational) and an increasing number of government initiatives to support research, training, and education in the area (again, both rational and not so rational). Irrespective of where one stands on the “hot” political issues associated with autism, there is little doubt that there has been a dramatic change in the general view of its epidemiology: prevalence has grown from approximately 0.1% to 0.8% of the population. With this rise in prevalence (curiously, with no substan-
tial evidence of a rise in incidence), there have been increasing demands for clinical and educational services. To meet these demands, both the clinical and scientific communities that focus on autism have taken a strong multidisciplinary and multimodal approach to research and practice. This leads to another irony — that pediatric neurologists have seized this moment to publish *Autism: A Neurological Disorder of Early Brain Development*, a book edited and written almost entirely by pediatric neurologists and for pediatric neurologists about a disorder that is anything but solely in the domain of pediatric neurology.

From the time of Leo Kanner’s groundbreaking 1943 clinical paper on autism, it has been largely assumed that autism is a neurobiologic disorder. Admittedly, there was a period of time when psychological and psychoanalytic constructs enjoyed popularity, but during most of the modern history of autism, there has been a rigorous search for the neural mechanisms underlying the disorder. And as Martha Denckla points out in her preface to the book, “The glaring gap in our knowledge about the social–emotional brain is like a ‘black hole’ in the book and accurately reflects the field of research it represents.” She goes on to explain, “It is not the fault of Roberto Tuchman that his important chapter called ‘The Social Deficit in Autism’ (Chapter 3) falls so short of its title.” Although the book has some other weaknesses, it is hardly bereft of knowledge.

This generally well-referenced book contains 19 chapters of widely varying length and quality. The strongest and longest chapter, “Atypical Sensory/Perceptual Responsiveness,” was written by Isabelle Rapin, an acknowledged expert on this curious problem that is a critical element of autism and similar developmental disorders. She systematically approaches various measurement and neurologic issues, leaving the reader with a solid, well-referenced foundation. And despite Denckla’s warning, I found Tuchman’s chapter on social deficit to be thoughtful and interesting.

Areas in which one would expect substantial expertise in pediatric neurology, however, are relatively weak. For example, it is unclear why there are two chapters addressing the topic of epilepsy and autism; there are, not surprisingly, redundancies in the information provided, but there are also important gaps. There is no discussion of childhood epilepsy as a genetic disorder that may be linked to the genesis of autism and virtually no mention of the complex questions related to the treatment of epilepsy in association with autism. Similarly, there are two seemingly disconnected chapters on sleep, and the discussion in both is superficial and lacking in clear treatment guidelines for this critical clinical problem.

Based on its title, this book would seem to have great potential. Unfortunately, aside from a few select chapters and excellent references, it is superficial and fails to capture the richness of the work in the field. Although it may serve as a useful reference from time to time, other books have been published that are better suited for inclusion in a library.

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**NEUROLOGY OF HEREDITARY METABOLIC DISEASES OF CHILDREN**


This latest edition of this book is an update of a very useful resource for pediatric neurologists, trainees in pediatric neurology or pediatric metabolic disease, and medical students. The book covers hereditary neurologic diseases in children more comprehensively than do standard pediatric or neurology textbooks, but it is not forbiddingly encyclopedic. The generally clear and uniform writing style and the judicious use of references enhance its value.

One of the book’s great strengths is the presentation of clinical material (chapters 3 through 5) according to the age of the child. This arrangement results in some redundancies, but the value of using age as an organizing tool is evident in the ease with which the book can be used for differential diagnosis. For each of the chosen ages, useful tables compare diseases and the specific signs or symptoms presented by patients (e.g., dystonia, seizures, ophthalmoparesis), giving the reader an overview by age and clinical presentation. These
summaries are complemented by thoughtfully chosen clinical examples. The descriptions of diseases have been updated by including the results of recent genetic and imaging tests. The discussions of the mitochondrial encephalopathies, Rett’s syndrome, and pantothenate kinase–associated degeneration disease are good examples of the inclusion of recent findings. Chapter 6, “Distinction between Hereditary Metabolic Diseases and Other Diseases of the Child’s Nervous System,” is important, but it may be confusing to some readers. Missing the distinction between static encephalopathies (e.g., cerebral palsy) and degenerative neurologic diseases (e.g., the early stage of metachromatic leukodystrophy) may be the most frequent mistake the experienced clinician makes in the diagnosis of children with complex encephalopathies. Important clinical observations are scattered throughout this chapter, but they would be more accessible if they were organized into short sections that followed each of the age-specific discussions of various disorders in chapters 3 through 5.

The last three chapters may be windows into the future of research on hereditary metabolic encephalopathies and their treatment. Chapter 7, “Visceral and Other Tissue Abnormalities Associated with Hereditary Metabolic Encephalopathies,” tabulates the non-neurologic manifestations of this group of diseases. Knowledge of organ abnormalities is helpful in the diagnosis of these diseases, and because the tissues are more accessible than the brain, their pathology and pathophysiology are easier to study. The next chapter, which discusses laboratory tests, has changed dramatically since the publication of the first edition of this book more than 20 years ago. Advances in imaging techniques and molecular biology will further change our nosologic system for the developmental encephalopathies and will increase the spectrum of diseases that are placed in the category of hereditary metabolic encephalopathies and neuropathies. The final chapter of the book, “Treatment and Prevention of Neurometabolic Disorders,” will expand as new technologies improve our understanding of the pathogenesis of these diseases and our ability to treat them. The authors are brave to venture into these promises.

Overall, this edition of Neurology of Hereditary Metabolic Diseases of Children is an important and ambitious contribution to the literature of this complex field. It is organized for clinical use and will be helpful to both trainees and experienced clinicians.

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**CORRECTIONS**

Treating COPD — The TORCH Trial, P Values, and the Dodo (February 22, 2007;356:851-4). The fifth sentence of the eighth paragraph (page 853) should have read “In the end, the trial failed to meet its goal: the P value for death from any cause was 0.052, which was higher than the prespecified value of 0.05,” rather than “prespecified value of 0.50.” The text has been corrected on the Journal’s Web site at www.nejm.org.

Into the Woods (March 1, 2007;356:943-7). Figure 1A (page 945) should have been reversed so that the arrow points to the left upper lobe rather than the right. The figure has been corrected on the Journal’s Web site at www.nejm.org. We regret the error.

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An 83-year-old healthy woman was admitted with episodes of nausea and vertigo that had increased in frequency over several months. Many of the episodes involved brief periods of unresponsiveness and staring spells. She did not report a history of seizures, head trauma, headache, or vestibular disease. The neurologic examination did not reveal papilledema or any other abnormalities. Computed tomography of the head showed a large (5 by 5 cm), well-circumscribed, and highly calcified extra-axial mass overlying the right temporal lobe. Electroencephalography showed mild slowing and occasional sharp waves in the right temporal area. A diagnosis of temporal-lobe seizures due to a meningioma was made. Surgical intervention was withheld in favor of medical management. The patient was treated with lamotrigine, and within 6 months her symptoms had resolved. She resides with her daughter but continues to live independently. She reports no further seizures and no new symptoms associated with the meningioma at 2 years of follow-up.

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