THIS WEEK IN THE JOURNAL

ARTICLE SUMMARIES

PERSPECTIVE

The Egg Trade — Making Sense of the Market for Human Oocytes
D. Spar

The Demise of the Blockbuster?
D. M. Cutler

ORIGINAL ARTICLES

MRI Evaluation of the Contralateral Breast in Women with Recently Diagnosed Breast Cancer
C. D. Lehman and Others

Effect of Torcetrapib on the Progression of Coronary Atherosclerosis
S. E. Nissen and Others

Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis
M. Y. Armanios and Others

Asthma Control during the Year after Bronchial Thermoplasty
G. Cox and Others

CLINICAL THERAPEUTICS

Varicella-Zoster Vaccine for the Prevention of Herpes Zoster
D. W. Kimberlin and R. J. Whitley

REVIEW ARTICLES

Current Concepts: Withdrawal of Albuterol Inhalers Containing Chlorofluorocarbon Propellants
L. Hendeles, G. L. Colice, and R. J. Meyer
Interventions Following Mass Violence and Disasters: Strategies for Mental Health Practice

Bioethics and Armed Conflict: Moral Dilemmas of Medicine and War

CORRECTIONS
Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy
Anna Behrens is 24 years old. Tall and slim, she is working toward her Ph.D. in art history at an Ivy League school. During her undergraduate years, Anna accumulated $27,000 in credit-card debt. In the fall of 2005, frustrated by her economic straits, Anna answered an advertisement in her university’s magazine promising $25,000 to a “tall, athletic woman” willing to “give a gift of life and love.” Anna visited the agent who had placed the ad, underwent medical tests at a fertility clinic, and met the couple that was searching for eggs. Through the agent, they offered her $20,000 plus medical expenses. Six weeks later, after 2 weeks of hormone injections, mood swings, and bloating, Anna returned to the clinic and had eight healthy oocytes removed. The couple took them, and Anna took her money. She will probably never know whether her eggs resulted in a successful pregnancy.

Encouraged, Anna went back to the agent in February 2006, offering to donate again. This time, as a “proven” donor, she received $22,000 from another couple, enough to eliminate her debt and pay for a Caribbean vacation.

Then, in September 2006, Anna saw another ad seeking healthy young women for egg donation. But this time, the oocytes were for research: using somatic-cell nuclear transfer (SCNT), scientists would attempt to use her eggs to generate a line of infinitely reproducing embryonic stem cells.

Intrigued, Anna answered the ad and learned that medically, the procedure was identical to what she’d already experienced. But there was no couple to meet this time and no baby to be produced. There was also no money. Instead, Anna was told apologetically, she would be reimbursed only for actual expenses — the bus fare, in her case, for trips to the in vitro fertilization (IVF) clinic.

Anna Behrens is not a real person. But her story plays out thousands of times annually in the United States. According to the Centers for Disease Control and Prevention, in 2003, at least 5767 babies were born after being conceived with donated eggs — an 11% increase from 2002. Since success rates for IVF using donated eggs averaged 30 to 50% in 2003, the number of IVF cycles performed that year using such eggs was considerably higher: 12,996. Some small fraction of the eggs were probably truly “donated,” given by friends or family members out of love. The rest were sold, for an average of about $5,000 per harvest. Eggs like Anna’s were relatively rare, bought by would-be parents willing to pay a premium for particular genetic traits.

For stem-cell science, however, the numbers and market were entirely different during the same
period. Most commercial laboratories in the United States were concentrating on adult or umbilical-cord stem cells, research trajectories that don’t depend on obtaining human embryos or oocytes. Most university laboratories were working either with the handful of stem-cell lines created before 2001, when the Bush administration’s prohibition on federal funding for embryonic stem-cell research went into effect, or with lines created from donated embryos left over from IVF treatment. Only a few laboratories had announced their intent to use donated human oocytes to generate specific stem-cell lines.

Such reluctance is understandable, for stem-cell science in the United States has been controversial since its inception. Some opponents liken the technology to cloning and therefore reject it; others vehemently disapprove of using embryos as research material. In such a heated environment, any proposal involving the use of human eggs will be incendiary, drawing new types of opponents into the political debate. Indeed, such opposition has already arisen, driven largely by women’s organizations worried about the health implications for egg donors and the potential for commodification inherent in egg donation.

To forestall these concerns, stem-cell scientists have been quick to promise never to purchase eggs. In April 2005, the National Academy of Sciences published its Guidelines for Human Embryonic Stem Cell Research, recommending that no payment be provided for donating oocytes for research. These recommendations were quickly adopted into law by states that explicitly permitted or promoted SCNT. Massachusetts legislation, for example, limits payment for egg donation for SCNT research to reimbursement for reasonable costs. In California, stem-cell researchers using state funds are prohibited from compensating egg donors for anything beyond direct expenses.

In theory, therefore, SCNT progress rests largely on the hope that one small segment of society will altruistically provide, free, the raw material for basic scientific research. It is a noble theory — but an implausible one. Why should young women — most of whom have not yet used their eggs to produce their own children and nearly all of whom have no chance of benefiting directly from the research — be expected to volunteer? And why should they categorically be denied any form of payment?

Answers to these questions typically focus on fears of exploitation, positing not reasons why women might volunteer but rather reasons why they shouldn’t receive any payment. One recent publication, for example, argues that “Offering payment [to egg donors] would likely induce economically vulnerable women to sell their eggs. . . . The potential for disproportionate recruitment of low-income women, women of color, and young college women . . . is high.”¹ If women were allowed to sell their eggs for research, worries another author, “[a] market in eggs for research would emerge, valuing women’s reproductive tissue over their well-being.”² These are legitimate concerns. But they mask the central contradiction highlighted by Anna’s story: in the United States, we already allow women to “donate” their eggs for profit. We allow them to undergo the same procedure and to undertake what is arguably a far more emotional endeavor — passing their genes to a child they will never know. How can we conclude that providing eggs for reproduction is less exploitative or dangerous than providing them for research?

We can’t. Which is why, as the demand for human oocytes grows, I believe that we need to reconfigure the debate over eggs and reexamine the issues raised by egg donation.

The most critical issue is the health of the women involved. If women are going to donate eggs, we must ensure that their health is not compromised. We need, therefore, to subject egg donation to far more scientific scrutiny than it currently receives. We need more longitudinal studies of the drugs involved in ovarian hyperstimulation, for example, more long-term follow-up of egg donors, and deeper analyses of the conditions under which dangerous complications occur. A recent report by the Institute of Medicine and the National Research Council confirms that egg donation is relatively safe.³ But five women are known to have died as a result of the procedure in the United Kingdom, and roughly 0.5 to 5% have reportedly had side effects ranging from respiratory distress to renal failure.⁴⁻⁵ We need to understand what went wrong in these cases and whether certain preconditions put women at particular risk.

Once these factors are better understood, a second obvious need is to ensure that potential donors are fully informed. Currently, there are no federal guidelines covering egg donation; donors thus learn
only what their brokers, clinics, or research laboratories choose to tell them. All live organ donors, by contrast, must undergo a formal process of informed consent overseen by the congressionally established Organ Procurement and Transplantation Network. Blood donors fall under the purview of the Food and Drug Administration and are both subject to the agency’s rules and protected by its consent provisions. Even participants in federally funded studies, some of whom undergo only an interview, are covered by federal regulations describing what kind of information they must receive and how their personal data will be protected. Certainly, egg donors deserve at least the same levels of information and protection, both of which could easily be provided by federal regulation regarding informed consent and by mandated insurance coverage.

A third task is to decide as a society whether we’re comfortable with providing monetary compensation for any form of egg “donation.” This decision should entail a thoughtful consideration of semantics and analogies. Too frequently, discussions of compensation are dismissed with facile references to other body parts. “If men can sell their sperm,” proponents say, “why can’t women sell their eggs?” Or, on the other side: “We don’t allow people to sell their kidneys. Why should they sell eggs?” But such lines of reasoning are dismissed with facile semantics and analogies. Too frequently, discussions of compensation are dismissed with facile references to other body parts. “If men can sell their sperm,” proponents say, “why can’t women sell their eggs?” Or, on the other side: “We don’t allow people to sell their kidneys. Why should they sell eggs?” But such lines of reasoning lack logic. Rather than accepting their implications, we need seriously to consider how we want to define eggs and whether we want women to be allowed to sell them.

Several countries that are engaged in stem-cell research have already launched this discussion and implemented egg-sale policies. In Britain, for example, where the research is supported and overseen by the government, women may donate eggs for both research and reproduction. But they cannot receive any payment beyond compensation for reasonable expenses and loss of earnings up to a predetermined limit. The result is predictable: a dearth of eggs. The country has therefore allowed “egg sharing,” whereby women undergoing IVF can donate excess eggs to other infertile women or to research in exchange for a discount on their own treatment. This practice has generated a small stream of eggs. But as its proponents quietly acknowledge, it is essentially hypocritical — redefining the interaction to avoid any reference to compensation. It also depends on the acquisition of eggs from women who — infertile and desperate for access to treatment — are arguably far less attractive than our fictional Anna Behrens.

In Singapore, another would-be stem-cell hub, egg donation is legal, but monetary compensation is limited to a small reimbursement for travel and personal expenses. In Israel, paid donation is illegal, but women undergoing assisted reproduction may share their eggs with other women. And in South Korea, since the Woo Suk Hwang scandal, egg donors cannot receive any financial reward or personal benefit.

These approaches seem relatively clear and (with the possible exception of Britain’s) internally consistent. The United States, by contrast, maintains the absurd inconsistency illustrated by the case of Anna Behrens: $20,000 for an egg used for reproduction; nothing for the same egg used for stem-cell research. Such a policy would make sense only if we deemed assisted reproduction socially more valuable than research. But this argument is not being made and perhaps could not logically stand, given that the alternative to assisted reproduction would often be adoption. Instead, opponents of egg selling tend to refer to the fears of commodification and the risks to donors — all of which, if valid, apply equally to the reproductive and research uses of eggs.

What we need, therefore, is a fresh debate on egg donation and a new set of policies. We need to consider the health risks and ways of identifying and mitigating them. We need to ensure that all potential donors are fully informed of these risks and fully protected against them. We need to make clear that the benefits of egg donation, for reproductive or research purposes, are complicated, and that few of these benefits will ever flow directly to the donor. At the moment, though, the politics of egg donation have blinded us to these real issues. We have not thought deeply about what makes sense for science, for women, and for society. Instead, we are only fighting about the price.

An interview with Dr. Spar and with Emily Galpern of the Center for Genetics and Society in Oakland, California, can be heard at www.nejm.org.

Dr. Spar is a professor of business administration at Harvard Business School, Boston.

The Demise of the Blockbuster?

David M. Cutler, Ph.D.

When Pfizer announced that it was halting clinical testing of its new cholesterol drug, torcetrapib, the company’s market value fell by $21 billion overnight. Ten thousand job cuts followed. The ongoing promise of nearly $3 billion in annual sales vanished when Merck pulled Vioxx (rofecoxib) from the shelves, and the company’s market value fell by $25 billion. For decades, blockbuster drugs have nourished Big Pharma, but it is increasingly uncertain whether they can be counted on to support the industry in the future.

Prescription medications are extremely costly to develop and market. The cost of bringing a new drug to market is estimated to be about $800 million — the amount that Pfizer, in fact, reports spending on the development of the now-defunct torcetrapib. Phase 3 trials alone cost an average of $86 million. Once a drug has been developed, production costs are typically low — in many cases, nickels per tablet. But while the drug is patent-protected, firms charge high prices, in part to compensate for the high cost of research and development and in part because the patent provisions give them the right to do so. Thus, the brand-name antidepressant Prozac (fluoxetine) cost $2.50 per capsule before its patent expired, whereas generic fluoxetine can now be purchased for $0.25 per capsule. It takes a big seller to make up for the $800 million development cost per new drug. The prize in the industry, therefore, is the blockbuster: a drug with $1 billion or more in annual global sales. The more blockbusters a firm has, the healthier it is. When the blockbusters dry up, the firm is in trouble.

Blockbusters have become increasingly important for the industry (see graphs). In 2000, 17 drugs brought in more than $1 billion each in global sales. In 2005, 94 drugs met this threshold. The aging of the population has played a big role in this evolution: Lipitor (atorvastatin), for instance, is a megablockbuster ($13 billion in annual sales) in part because aging baby boomers are at increasing risk for coronary disease. And increasing incomes enable people to afford “lifestyle” medications as well as essential ones. Since both of these trends are likely to continue, the industry’s future could be bright.

But there are storm clouds as well — trends suggesting that the blockbuster model may not be sustainable. It may not go the way of bloodletting, but perhaps the house call: once the norm, it is now rare. Several factors are at work. One is economic: as companies become better at discovering and producing medications, a drug is rarely the only one in its class. In the 1970s, a typical drug in a new class enjoyed 10.2 years of market exclusivity. By the late 1990s, a new drug had only 1.2 years. Although it is fashionable to deride “me-too” drugs, they serve a valuable purpose for consumers: they help to keep prices low. Imagine if torcetrapib had been successful, but a similar drug from another firm had appeared shortly after, with virtually the same safety and efficacy profile. Insurers and payers would have promised the bulk of their business to the cheaper one, and prices could have fallen markedly.

Historically, price competition in pharmaceuticals has been limited; U.S. insurers and patients generally paid whatever the drug cost. But the high price of drugs makes the need for competition more urgent. Patients’ copayments for drugs categorized as “nonpreferred” in their three-tier formularies are increasing greatly and could rise even higher if consumers move to high-deductible health plans in large numbers. Already, generic versions of Zocor (simvastatin) are reportedly taking significant business from Lipitor.

The second issue is equity and access. Even with Medicare’s prescription drug benefit, not everyone can afford prescription medications. Millions of elderly people will continue to pay thousands of dollars annually for medications under the Medicare benefit. A single drug in the third tier of a formulary might come with an out-of-pocket cost of $600 to $960 per year. And the uninsured find many drugs too expensive. If current cost trends continue, Americans are likely to lose their tolerance for paying substantially more than Canadians do for the same brand-name drugs, and Medicare may begin to demand its own discounts.

The third factor is scientific. The blockbuster model relies on the proposition that the same drug is good for everyone — that one size fits all. But even drugs with similar average efficacy do not have the same effect for all. Although rates of remission among patients...
with depression treated with the various selective serotonin-reuptake inhibitors (SSRIs) are all about 50%, the response to each drug is idiosyncratic and unpredictable. Someday, genetic science may tell us why some patients are more responsive than others. When that happens and drugs can be targeted more accurately to patients likely to have the desired response, the market for any particular SSRI will shrink.

There will be ways of offsetting the resulting losses. A drug known to be effective in only some patients could command a higher price for those patients (as long as no me-too drugs emerged to force prices down) and could be prescribed with greater assurance. It might cost companies less to develop multiple products in a single class for different segments of the market than to develop completely unrelated products for entirely new markets. Still, it is difficult to envision the blockbuster model as we know it surviving the era of stratified (or perhaps personalized) medicine.4

What are the implications for a less pervasive blockbuster model? A central issue is whether pharmaceutical firms would curtail their investments in research and development. Clearly, manufacturers would stand to lose from such a change, but so might patients. Prescription medications are expensive, but they are still a good value. Even today, they account for only 10% of total medical spending. Spending on hospital care is three times as great, and spending on physician and clinical services twice as great. Furthermore, the cost-effectiveness ratio for prescription medications is extremely favorable. According to one study, the median cost of a drug was $11,000 per quality-adjusted life-year, as compared with $140,000 per quality-adjusted life-year for medical procedures.5 The ultimate effect on pharmaceutical research and development will depend on many factors, including the costs of clinical testing and the reimbursement environment in the United States and abroad, but the role of the blockbuster is one significant factor.

A decline in the blockbuster’s importance might also change the nature of physician prescribing. In the blockbuster era, prescribing was sometimes formulaic. If the patient had high cholesterol, the prescription was Lipitor, or perhaps Zocor or Vytorin (ezetimibe and simvastatin), depending on the formula. In the new era, physicians might have to conduct genetic or biochemical analysis to determine which medication is the appropriate one. Just as physicians have learned to continue to follow patients taking antidepressants that are not universally effective, they might someday need to conduct extensive testing before prescribing a medication. The role of the doctor could thus become even more important than it is today.

Finally, a reduced presence of the blockbuster will heighten the need for postlaunch safety and efficacy studies. As molecules are increasingly targeted to niche markets, pre-approval study populations will necessarily shrink, and the need to monitor how drugs actually work after approval will intensify. To date, postlaunch monitoring has been inconsistent.

Blockbusters have long sustained the pharmaceutical industry. Whether they can continue to do so is a subject of considerable debate. If the blockbuster declines in importance, the clinical experience may change in fundamental ways.

Dr. Cutler is a professor of economics at Harvard University, Cambridge, MA.


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MRI Evaluation of the Contralateral Breast in Women with Recently Diagnosed Breast Cancer

Up to 10% of women with a diagnosis of unilateral breast cancer have cancer in the contralateral breast, despite negative clinical and mammographic examinations. This study investigated the use of MRI examination of the contralateral breast in women with a diagnosis of unilateral breast cancer and negative clinical and mammographic examinations. MRI detected occult cancer in the contralateral breast in about 3% of these women. All of the cancers were early stage, without evidence of spread to the lymph nodes or beyond.

See P. 1295; Editorial, P. 1362; CME, P. 1391

Original Article

Effect of Torcetrapib on the Progression of Coronary Atherosclerosis

In this 24-month clinical trial, torcetrapib, a cholesteryl ester transfer protein inhibitor, failed to cause regression of coronary atherosclerosis, as seen on intravascular ultrasonography, even though levels of high-density lipoprotein cholesterol were markedly elevated. The drug was also associated with an elevation in blood pressure, and the entire torcetrapib research program has been suspended.

See P. 1304; Editorial, P. 1364

Original Article

Mutant Telomerase in Familial Idiopathic Pulmonary Fibrosis

Mutations affecting both components of the telomerase enzyme, hTERT and hTR, are associated with familial idiopathic pulmonary fibrosis, and carriers of such mutations have shorter telomeres than do noncarrier family members. This finding suggests that the disease may be triggered by a loss of alveolar cells, the progenitors of which may be limited by short telomeres.

See P. 1317

Original Article

Bronchial Thermoplasty in Asthma

Asthmatic exacerbations result in part from constriction of airway smooth muscle. In this controlled trial, the use of bronchoscopically delivered thermoplasty to reduce the mass of airway smooth muscle resulted in fewer exacerbations among subjects with moderate or severe asthma. The incidence of adverse events was higher among subjects undergoing bronchial thermoplasty than among control subjects during the first 3 weeks after treatment.

See P. 1327; Editorial, P. 1367

Clinical Therapeutics

Varicella–Zoster Vaccine for the Prevention of Herpes Zoster

A 64-year-old man in good general health presents to his internist for a routine examination. In a large clinical trial, the varicella–zoster vaccine reduced the incidence of herpes zoster by 51% and the incidence of postherpetic neuralgia by 67%. Should he receive this vaccine?

See P. 1338; CME, P. 1389

Current Concepts

Withdrawal of Albuterol Inhalers Containing Chlorofluorocarbon Propellants

The Montreal Protocol requires limitation of the use of devices powered by chlorofluorocarbons (CFCs), which reduce stratospheric ozone levels. Albuterol, a medication commonly used for the treatment of asthma that is delivered by metered-dose inhalers with CFCs as propellants, will be withdrawn from the U.S. market by December 2008. This review article summarizes useful information about albuterol in metered-dose inhalers with non-CFC propellants and discusses associated economic issues.

See P. 1344; CME, P. 1390

Case Records of the Massachusetts General Hospital

A 55-Year-Old Man Impaled in a Rowing Accident

A 55-year-old man was sculling when his boat collided with an eight-person shell; the prow of the larger boat entered his lower back and exited through his abdomen, throwing him into the water. He was taken to this hospital, where the trauma surgery team took over his care. Members of the team discuss the problems of traumatic abdominal and orthopedic injuries and the role of trauma systems.

See P. 1353

Clinical Implications of Basic Research

Parsing Pulmonary Fibrosis

The signaling molecule caveolin-1 provides protection against pulmonary fibrosis in a mouse model and counters the profibrotic effects of transforming growth factor β1 (TGF-β1). That TGF-β1 negatively affects telomeres is consistent with the association between mutant telomerase and familial idiopathic pulmonary fibrosis reported elsewhere in this issue of the Journal (pages 1317–26).

See P. 1370
MRI Evaluation of the Contralateral Breast in Women with Recently Diagnosed Breast Cancer

Constance D. Lehman, M.D., Ph.D., Constantine Gatsonis, Ph.D., Christiane K. Kuhl, M.D., R. Edward Hendrick, Ph.D., Etta D. Pisano, M.D., Lucy Hanna, M.S., Sue Peacock, M.S., Stanley F. Smazal, M.D., Daniel D. Maki, M.D., Thomas B. Julian, M.D., Elizabeth R. DePeri, M.D., David A. Bluemke, M.D., Ph.D., and Mitchell D. Schnall, M.D., Ph.D., for the ACRIN Trial 6667 Investigators Group*

A b s t r a c t

BACKGROUND
Even after careful clinical and mammographic evaluation, cancer is found in the contralateral breast in up to 10% of women who have received treatment for unilateral breast cancer. We conducted a study to determine whether magnetic resonance imaging (MRI) could improve on clinical breast examination and mammography in detecting contralateral breast cancer soon after the initial diagnosis of unilateral breast cancer.

METHODS
A total of 969 women with a recent diagnosis of unilateral breast cancer and no abnormalities on mammographic and clinical examination of the contralateral breast underwent breast MRI. The diagnosis of MRI-detected cancer was confirmed by means of biopsy within 12 months after study entry. The absence of breast cancer was determined by means of biopsy, the absence of positive findings on repeat imaging and clinical examination, or both at 1 year of follow-up.

RESULTS
MRI detected clinically and mammographically occult breast cancer in the contralateral breast in 30 of 969 women who were enrolled in the study (3.1%). The sensitivity of MRI in the contralateral breast was 91%, and the specificity was 88%. The negative predictive value of MRI was 99%. A biopsy was performed on the basis of a positive MRI finding in 121 of the 969 women (12.5%), 30 of whom had specimens that were positive for cancer (24.8%); 18 of the 30 specimens were positive for invasive cancer. The mean diameter of the invasive tumors detected was 10.9 mm. The additional number of cancers detected was not influenced by breast density, menopausal status, or the histologic features of the primary tumor.

CONCLUSIONS
MRI can detect cancer in the contralateral breast that is missed by mammography and clinical examination at the time of the initial breast-cancer diagnosis. (ClinicalTrials.gov number, NCT00058058.)

*Members of the American College of Radiology Imaging Network (ACRIN) Trial 6667 Investigators Group are listed in the Appendix.
A woman with unilateral breast cancer has an increased risk of having cancer in the contralateral breast. In the 1990s, the role of mammography in improving the detection of contralateral cancers at the time of the initial diagnosis of breast cancer was firmly established; as compared with clinical breast examination alone, mammography resulted in a 1 to 3% increase in the number of cancers detected. Despite normal findings on clinical and mammographic examination of the contralateral breast at the time of the initial breast-cancer diagnosis, however, contralateral cancer was subsequently detected in up to 10% of women.

When contralateral cancer is diagnosed after the initial treatment, the woman must undergo a second round of cancer therapy rather than the single round that would have been administered if the contralateral cancer had been detected at the time of the initial diagnosis.

The importance of clinical breast examination and mammography in the diagnostic workup of a woman with recently diagnosed breast cancer is not disputed. However, mammography and clinical breast examination have limitations — both methods yield false negative results. A recent large study showed that screening magnetic resonance imaging (MRI) can improve on mammography by detecting otherwise occult cancers in 1.2% of women at high risk. However, this study did not include women with a current diagnosis of breast cancer. Preliminary studies have suggested that MRI can detect otherwise occult contralateral breast cancers in an average of 5% of women with a recent diagnosis of breast cancer. The rate of detection for tumors not identified by other means ranged from 3 to 24%, the specificity of MRI was variable, and the studies lacked follow-up data to confirm the negative predictive values of MRI in such women. We conducted a study to determine the number of clinically and mammographically occult cancers in the contralateral breast that could be detected by MRI in women with recently diagnosed unilateral breast cancer.

**METHODS**

The trial was conducted by the American College of Radiology Imaging Network (ACRIN), funded by the National Cancer Institute, and monitored by a data and safety monitoring board. It was open to all interested sites that were approved by ACRIN through a general qualifying application and a protocol-specific application. The sites ranged from academic institutions to private practices. Between April 1, 2003, and June 10, 2004, a total of 1007 women with a recent diagnosis of unilateral breast cancer were enrolled at 25 sites.

Participating radiologists had to have interpreted a minimum of 50 breast MRI scans and had to have performed at least five magnetic resonance-guided breast biopsies. All participating facilities obtained approval for the study from their institutional review boards, and written informed consent was obtained from all patients.

**PATIENTS**

Women were eligible to participate in the study if they were 18 years of age or older and had received a diagnosis of unilateral breast cancer within 60 days before the study MRI was performed. Since the study was designed not to compare mammography with MRI but to determine the additional number of cancers detected by means of MRI after clinical and mammographic examination of the contralateral breast, all women were required to have had normal clinical and mammographic findings in the contralateral breast within 90 days before enrollment. Women were excluded from the study if they had undergone breast MRI within 12 months before enrollment, if they were pregnant, or if they had a contraindication for MRI (e.g., an implanted magnetic device or severe claustrophobia). Additional exclusion criteria were a breast-cancer diagnosis made more than 60 days before enrollment or chemotherapy or hormonal therapy for breast cancer within 6 months before enrollment.

**DATA COLLECTION**

All participants underwent dynamic, contrast-enhanced breast MRI. Minimum standard criteria were required for each MRI study performed: a 1.5-T or larger magnet, a dedicated breast-surface coil, and one image obtained before and two images obtained after the administration of contrast material, with three-dimensional, T1-weighted, gradient-echo sequences (reception time, <60 msec; echo time, <20 msec). Initial and delayed images were obtained within 4 and 8 minutes after the injection of contrast material. Spatial-resolution criteria included voxels smaller than 0.9 mm in the frequency-encoding direction,
smaller than 1.8 mm in the phase-encoding direction, and 3 mm or smaller in the slice direction, providing full coverage of the breast.

All examinations were interpreted according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). The initial MRI assessment was classified on a six-point scale (0, “needs additional imaging evaluation”; 1, “negative”; 2, “benign”; 3, “probably benign”; 4, “suspicious abnormality”; and 5, “highly suggestive of malignancy”). For examinations scored as 0 or 3, additional imaging was performed to determine the final BI-RADS assessment. For purposes of receiver-operating-characteristic (ROC) curve analysis, readers also rated the initial study MRI on a five-point malignancy scale (with a score of 1 denoting “definitely not malignant” and a score of 5 denoting “definitely malignant”). A diagnosis of cancer was based on histologic examination of a biopsy specimen and included all cases of invasive carcinoma or ductal carcinoma in situ.

Cancer status was followed for 365 days after the study MRI. Results of all breast-imaging tests, clinical examinations, and biopsies and surgeries were documented. To establish a reference standard, the study participants were classified as positive for cancer if a breast cancer was histologically verified within 365 days after the initial study MRI, and negative for cancer if the study records, including the 1-year follow-up, showed no diagnosis of cancer within that period. The details of all cancers diagnosed during the study were recorded, including the size and histologic features of the tumor and tumor–node–metastasis staging.

**Statistical Analysis**

Data were analyzed at the Center for Statistical Sciences at Brown University (Providence, RI), which serves as the biostatistics center for all ACRIN trials. The primary aim of the study was to determine the diagnostic yield of breast MRI, defined as the proportion of women with a recently diagnosed unilateral breast cancer and negative clinical and mammographic examinations of the contralateral breast in whom cancer in that breast was detected by MRI and histologically confirmed. The secondary aims included estimation of the sensitivity, specificity, negative predictive value, and positive predictive value of MRI and the associated positive biopsy rate; estimation of the ROC curve for MRI; and assessment of the diagnostic yield, sensitivity, specificity, negative predictive value, positive predictive value, and associated positive biopsy rate according to mammographic density (fatty vs. dense), menopausal status (premenopausal or perimenopausal vs. postmenopausal), and the type of index cancer (invasive vs. in situ and lobular vs. nonlobular).

The final BI-RADS MRI assessment score was used to derive estimates of the diagnostic yield, sensitivity, specificity, negative predictive value, positive predictive value, and associated positive biopsy rate. This score was equal to the initial score if the initial score was 1, 2, 4, or 5. Participants with an initial score of 0 or 3 were assigned a final score that took into account the results of the workup after the initial MRI. For estimation of the diagnostic yield, sensitivity, and specificity, a final BI-RADS MRI score of 1, 2, or 3 was considered to be negative, and a final score of 0, 4, or 5 was considered to be positive. The same classification of the test result was used to estimate the positive predictive value of a final positive score.

Diagnostic test data from all participating readers for the primary and secondary analyses were pooled. The 95% confidence intervals for the binary test measures (diagnostic yield, sensitivity, specificity, negative predictive value, positive predictive value, and positive biopsy rate) were derived with the use of the normal approximation of the binomial distribution. Exact intervals were computed and reported when the asymptotic approximation was not sufficiently accurate. All reported P values are two-sided. The differences in the diagnostic yield, sensitivity, and specificity were used to compare subgroups. Ratios were used to compare the negative predictive values, positive predictive values, and positive biopsy rates in subgroups. Approximate confidence intervals for the ratios were computed. The Bonferroni correction was used to assess significance in the comparisons of measures of performance among subgroups. For each performance measure, four comparisons were made; thus, a P value of less than 0.0125 was considered to indicate statistical significance. Computations were carried out with the use of SAS software.
The degree of suspicion recorded in the report on the initial MRI was used to derive a ROC curve. A binomial model was used to estimate and plot the ROC curve, as implemented with Stata software.24

RESULTS

STUDY POPULATION

A total of 1007 women were enrolled in the trial, 20 of whom were subsequently determined to be ineligible. Four eligible participants withdrew from the study and 14 who did not undergo the study MRI examination were excluded. Thus, the study group comprised 969 participants (98.2% of the eligible women). Table 1 lists the characteristics of all eligible women and of those included in the study group. Table 1 also shows the histologic features of the index breast cancer (the cancer diagnosed before enrollment). The major types were infiltrating ductal carcinoma (in 58.3% of the women) and ductal carcinoma in situ (20.2%).

Table 1. Characteristics of Eligible Patients and Participants in the Study.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Eligible Patients (N=987)</th>
<th>Study Participants (N=969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>53.4±11.4</td>
<td>53.3±11.4</td>
</tr>
<tr>
<td>Ethnic group — no. (%)</td>
<td></td>
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<tr>
<td>Hispanic or Latino</td>
<td>39 (4.0)</td>
<td>38 (3.9)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>942 (95.4)</td>
<td>925 (95.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (0.6)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>3 (0.3)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>23 (2.3)</td>
<td>23 (2.4)</td>
</tr>
<tr>
<td>Black</td>
<td>49 (5.0)</td>
<td>48 (5.0)</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>White</td>
<td>903 (91.5)</td>
<td>887 (91.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (1.4)</td>
<td>14 (1.4)</td>
</tr>
<tr>
<td>Menopausal status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal or perimenopausal</td>
<td>418 (42.4)</td>
<td>414 (42.7)</td>
</tr>
<tr>
<td>Postmenopausal (natural or surgical menopause)</td>
<td>565 (57.2)</td>
<td>552 (57.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>No. of first-degree relatives with breast cancer — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>787 (79.7)</td>
<td>774 (79.9)</td>
</tr>
<tr>
<td>1</td>
<td>182 (18.4)</td>
<td>179 (18.5)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>12 (1.2)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (0.6)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>No. of relatives (first-degree or other) with breast cancer — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>615 (62.3)</td>
<td>606 (62.5)</td>
</tr>
<tr>
<td>1</td>
<td>253 (25.6)</td>
<td>249 (25.7)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>113 (11.4)</td>
<td>109 (11.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (0.6)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Histologic features of index cancer — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>577 (58.5)</td>
<td>565 (58.3)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>198 (20.0)</td>
<td>196 (20.2)</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>102 (10.3)</td>
<td>101 (10.4)</td>
</tr>
<tr>
<td>Infiltrating carcinoma with ductal and lobular features</td>
<td>61 (6.2)</td>
<td>60 (6.2)</td>
</tr>
<tr>
<td>Other‡</td>
<td>49 (5.0)</td>
<td>47 (4.9)‡</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Ethnic group or race was reported by the patients. Numbers may not sum to 100 because of rounding.
† Race was self-reported.
‡ Other cancers included 16 mucinous cancers, 10 carcinomas not otherwise specified, 10 invasive cancers, not otherwise specified, 7 tubular cancers, 1 medullary tumor, 1 case of Paget’s disease, 1 squamous-cell carcinoma, and 1 unknown.
One-year follow-up information was available for 939 of the 969 women. The results of a biopsy, clinical breast examination, or additional imaging (mammographic, ultrasound, or repeat MRI) performed 10 to 14 months after the initial study MRI were recorded for 899 of the 969 women. For 40 of the 969 women, the results of a clinical breast examination, a biopsy, or additional imaging performed between 6 and 10 months after the initial study MRI were recorded.

Breast Cancers
Among the 969 women, a total of 33 contralateral breast tumors were diagnosed within 365 days after entry into the study. Of these 33 tumors, 30 were diagnosed as the result of a positive breast MRI examination, 1 was diagnosed by examination of a mastectomy specimen from a woman with MRI findings that were interpreted as BI-RADS 3 (probably benign), and 2 were discovered in prophylactic mastectomy specimens from women with MRI findings that were interpreted as BI-RADS 1 (negative). The three tumors associated with a BI-RADS 1 or BI-RADS 3 score (indicating a false negative result of MRI) were pure ductal carcinomas in situ and were 1, 3, and 4 mm in diameter.

Diagnostic Performance of Breast MRI
MRI detected biopsy-proven contralateral tumors in 30 of the 969 women, for a diagnostic yield of MRI, after negative findings on mammographic and clinical breast examination, of 3.1% (95% confidence interval [CI], 2.0 to 4.2). In the entire study population, the estimated sensitivity of breast MRI was 91% (95% CI, 76 to 98) and the specificity was 88% (95% CI, 86 to 90). The negative predictive value of MRI was 99% (95% CI, 99 to 100). The estimated positive predictive value of a positive MRI examination was 21% (95% CI, 14 to 27) (Table 2). On the basis of a positive MRI examination, a biopsy was recommended for 135 of the 969 women (13.9%), and 121 of them underwent a biopsy. Examination of specimens from these 121 biopsies detected 30 cancers (24.8%). Among the women with a positive MRI examination who did not undergo a recommended biopsy, the lesion was no longer visible on subsequent imaging in nine women, four women declined the procedure, and in one woman it was contraindicated. A total of 91 of 969 women with a positive MRI finding underwent a biopsy that detected a benign lesion.

As Table 2 shows, there were no significant differences in the diagnostic yield, sensitivity, or negative predictive value of MRI according to breast density (fatty vs. dense), menopausal status (premenopausal or perimenopausal vs. postmenopausal), or the histologic features of the index cancer (invasive vs. in situ and lobular vs. non-lobular). The specificity was significantly higher among postmenopausal women than among premenopausal or perimenopausal women (91% vs. 84%, P = 0.002; 95% CI for the difference, 2.5 to 11.1). Similarly, the positive predictive value was higher in the postmenopausal group than in the premenopausal or perimenopausal group (31% vs. 11%; ratio, 2.83; 95% CI for ratio, 1.22 to 6.58; P = 0.006), as was the positive biopsy rate (35% vs. 14%, ratio, 2.62; 95% CI for ratio, 1.14 to 6.0; P = 0.009).

The estimated mean (±SE) area under the ROC curve for MRI was 0.94±0.02 (95% CI, 0.90 to 0.98) for the entire study cohort (Table 2 and Fig. 1). There were no significant differences in the areas under the ROC curve for any of the paired subgroup comparisons (Table 2).

Tumor Characteristics
Table 3 provides details of the 30 otherwise occult breast tumors that were detected by MRI. Of these 30 tumors, 18 were invasive carcinomas and 12 were ductal carcinomas in situ. Ductal carcinoma was the most common invasive cancer (accounting for 67% of invasive tumors), followed by invasive lobular carcinoma (22%) and two cases of tubular carcinoma. The average diameter of the invasive tumors was 10.9 mm (range, 1 to 42). None of the 30 cancers diagnosed in the study were associated with detectable metastases, and all lymph nodes were negative for metastases in 27 of the 30 women with tumors in the contralateral breast; information about nodal status was not available for the other 3 women, all of whom had invasive disease. A total of 96.7% of the cancers were stage 0 or stage 1. The one stage 2 cancer was a 4.2-cm, node-negative, infiltrating lobular carcinoma.

Discussion
The current standard practice for evaluating the contralateral breast in women with a recent diagnosis of breast cancer is to perform a clinical breast examination and mammography. In this prospective study, we estimated the additional
Table 2. Performance of Breast MRI According to Breast Density, Menopausal Status, and Histologic Features of the Index Cancer.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cancers Detected*</th>
<th>Sensitivity†</th>
<th>Specificity‡</th>
<th>Negative Predictive Value§</th>
<th>Positive Predictive Value¶</th>
<th>Positive Biopsy Rate‖</th>
<th>Fitted AUC**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Total No. (%)</td>
<td>Standard Error (95% CI)</td>
<td>No./Total No. (%)</td>
<td>Standard Error (95% CI)</td>
<td>No./Total No. (%)</td>
<td>Standard Error (95% CI)</td>
<td>No./Total No. (%)</td>
</tr>
<tr>
<td>All participants</td>
<td>30/969 (3)</td>
<td>1 (2–4)</td>
<td>30/33 (91)</td>
<td>5 (76–98)</td>
<td>822/936 (88)</td>
<td>1 (86–90)</td>
<td>822/825 (99)</td>
</tr>
<tr>
<td>Breast density</td>
<td>Fatty</td>
<td>9/299 (3)</td>
<td>1 (1–5)</td>
<td>9/9 (100)</td>
<td>0 (100–100)</td>
<td>264/290 (91)</td>
<td>2 (88–94)</td>
</tr>
<tr>
<td>Dense</td>
<td>20/666 (3)</td>
<td>1 (2–4)</td>
<td>20/23 (87)</td>
<td>7 (66–97)</td>
<td>555/643 (86)</td>
<td>1 (84–89)</td>
<td>555/558 (99)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Premenopausal or perimenopausal</td>
<td>8/414 (2)</td>
<td>1 (1–3)</td>
<td>8/10 (80)</td>
<td>13 (44–97)</td>
<td>339/404 (84)</td>
<td>2 (80–87)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>22/552 (4)</td>
<td>1 (2–6)</td>
<td>22/23 (96)</td>
<td>4 (78–100)</td>
<td>480/529 (91)</td>
<td>1 (88–93)</td>
<td>480/481 (99)</td>
</tr>
<tr>
<td>Histologic features of index cancer</td>
<td>Infiltrating ductal carcinoma</td>
<td>19/565 (3)</td>
<td>1 (2–5)</td>
<td>19/20 (95)</td>
<td>5 (75–100)</td>
<td>478/545 (88)</td>
<td>1 (85–90)</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>6/101 (6)</td>
<td>2 (1–11)</td>
<td>6/6 (100)</td>
<td>0 (100–100)</td>
<td>83/95 (87)</td>
<td>3 (81–94)</td>
<td>83/83 (100)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>5/196 (3)</td>
<td>1 (0.3–5)</td>
<td>5/7 (71)</td>
<td>17 (29–96)</td>
<td>170/189 (90)</td>
<td>2 (86–94)</td>
<td>170/172 (99)</td>
</tr>
</tbody>
</table>

* The first number is the number of cancers detected, and the second is the total number of patients. Numbers may not sum to 100 because of rounding.
† The first number is the number of true positive results, and the second is the total number of patients with tumors in the contralateral breast.
‡ The first number is the number of true negative results, and the second is the total number of patients without tumors in the contralateral breast.
§ The first number is the number of true positive results, and the second is the total number of true positive and false positive results.
¶ The first number is the number of true negative results, and the second is the total number of true negative and false negative results.
‖ The first number is the number of biopsy-confirmed results, and the second is the total number of biopsies performed.
** AUC denotes the area under the ROC curve.
diagnostic yield of MRI in such women. Among 969 women with a recent diagnosis of breast cancer and normal results of clinical breast examination and mammographic studies, 30 contralateral cancers were detected on MRI (18 invasive cancers and 12 ductal carcinomas in situ), for a diagnostic yield of 3.1%, with a sensitivity of 91%. In comparison, a recent assessment of mammographic and MRI screening in 1909 high-risk women documented 22 cancers that were detected only by means of MRI; the additional diagnostic yield of MRI over mammography was 1%, with a sensitivity of 80%.25–27

We did not find that breast MRI had a low specificity, as previously reported.25–27 The specificity of MRI in our study was 88%; a biopsy was recommended on the basis of a positive MRI in 13.9% of the women, and 24.8% of the biopsies resulted in a diagnosis of breast cancer. The overall high accuracy of MRI (as measured by the estimated area under the ROC curve of 0.94) may reflect improved technology or improved interpretation of the results, especially in regard to how to distinguish benign from malignant patterns of enhancement on MRI scans. Our results should be widely applicable, since the participating sites represent a range of radiology practices, from academic centers to community practices, and a range of expertise in interpreting breast MRI studies, from extensive experience to moderate experience.

The negative predictive value of MRI in the population we studied was extremely high (99%). The risk of an occult cancer in the contralateral breast 1 year after a negative MRI was estimated at 0.3%, and all of the cancers that were detected at that time were ductal carcinoma in situ and were 4 mm or less in diameter. This information may be helpful to women and their physicians in discussing the relative value of bilateral mastectomy when only unilateral cancer is diagnosed after breast MRI. Some women with a diagnosis of unilateral breast cancer choose prophylactic mastectomy of the contralateral breast,28,29 but negative findings on preoperative MRI and mammographic studies might reduce the number of unnecessary mastectomies.

In our study, all of the cancers that were detected by means of MRI were node-negative, and 40% were ductal carcinomas in situ. The success of screening programs for breast cancer lies in their ability to detect early cancer, before it has spread to lymph nodes or metastasized to distant sites. Recent studies provide support for the benefit of detecting ductal carcinoma in situ, since this tumor is likely to progress to invasive disease if left untreated.30–32 In addition to early detection of in situ or node-negative invasive disease in the contralateral breast, MRI, if positive, can

---

**Table 3. Histologic Features of Cancers in the Contralateral Breast Detected on MRI and Size and Stage of Invasive Tumors.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic features — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>In situ carcinoma</td>
<td>12/30 (40)</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>18/30 (60)</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>12/18 (67)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>4/18 (22)</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>2/18 (11)</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td></td>
</tr>
<tr>
<td>Mean diameter — mm (range)</td>
<td>10.9 (1–42)</td>
</tr>
<tr>
<td>TNM stage — no./total no. (%)*</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>17/18 (94)</td>
</tr>
<tr>
<td>T2</td>
<td>1/18 (6)</td>
</tr>
<tr>
<td>NX (unknown)</td>
<td>3/18 (17)</td>
</tr>
<tr>
<td>N0</td>
<td>15/18 (83)</td>
</tr>
<tr>
<td>M0</td>
<td>18/18 (100)</td>
</tr>
</tbody>
</table>

* TNM denotes tumor–node–metastasis.
lead to simultaneous treatment of synchronous cancers rather than multiple treatments on separate occasions.

Our study shows that MRI can improve the detection of cancer in the contralateral breast when added to a thorough clinical breast examination and mammographic evaluation at the time of the initial diagnosis of breast cancer. The increased rate of detection of cancer comes with a false positive rate of 10.9% and a relatively low risk of detecting benign disease on biopsy (9.4%). The current cost of MRI precludes its widespread use in general populations, but this imaging tool appears to improve the detection of cancer in women at increased risk, such as women with a recent diagnosis of breast cancer.

Supported by grants from the National Cancer Institute (CA 80098 and CA 79778).

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

We thank the many people at the headquarters of ACRIN and at the recruiting sites for their important contributions to the study; the dedicated radiologists and research associates at the clinical sites; and Bruce Hillman, Cynthia Olson, Diane Guay, Charles Appar, Steve King, Sophia Sabina, Anthony Levering, Cheryl Crozier, Karon Boparai, Sharlene Snowdon, Rob Sole, Marianne Rahme, Glenn Gabrielli, Jo-Anne D’Amato, Chris Stewart, and Peggy Devine.

APPENDIX

The following persons served as principal investigators at the ACRIN 6667 clinical sites: Allegheny-Singer Research Institute, Pittsburgh — T. Julian, W. Poller; Boca Raton Community Hospital, Boca Raton, FL — K. Schilling; Clinical Radiologists, Springfield, IL — C. Neal, L. Wichterman; Elizabeth Wende Breast Clinic, Rochester, NY — P. Seifert; Hartford Hospital, Hartford, CT — M. O’Laughlin; Johns Hopkins University, Baltimore — D. Bluemink, S. Kawamoto; Mayo Clinic, Jacksonville, FL — E. DePerri; Northwestern University Medical School, Chicago — E. Hendrick, J. Wolfman; Porter Adventist Hospital, Denver — S. Smazal, D. Thickman; Scottsdale Medical Imaging, Scottsdale, AZ — R. Korn, D. Maki, C. Whafrill; St. Elizabeth Health Center, Youngstown, OH — A. Cook; Sunnybrook and Women’s College, Toronto — P. Causer; Thomas Jefferson University Hospital, Philadelphia — V. Rao, C. Piccoli; University of Arkansas for Medical Sciences, Fayetteville — E. Ferris, S. Harms; University of Bonn, Bonn, Germany — C. Kuhl; University of California at Los Angeles Medical Center, Los Angeles — N. DeBruhl; University of California, San Francisco, San Francisco — N. Hylton; University of Cincinnati, Cincinnati — M. Mahoney; University of North Carolina at Chapel Hill, Chapel Hill — E. Pisano; University of Pennsylvania Medical Center, Philadelphia — M. Schnall, S. Weinstein; University of Southern California, Los Angeles — S. Keekarsa; University of Texas Southwestern Medical Center, Dallas — P. Weatherall; University of Virginia Medical Center, Charlottesville — G. DeAngelis; University of Washington, Seattle — C. Lehman; and Wayne State University, Detroit — T. Li, R. Soulun.

REFERENCES


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Effect of Torcetrapib on the Progression of Coronary Atherosclerosis

Steven E. Nissen, M.D., Jean-Claude Tardif, M.D.,
Stephen J. Nicholls, M.B., B.S., Ph.D., James H. Revkin, M.D.,
Charles L. Shear, Dr.P.H., William T. Duggan, Ph.D., Witold Ruzyllo, M.D.,
William B. Bachinsky, M.D., Gregory P. Lasala, M.D., and E. Murat Tuzcu, M.D.,
for the ILLUSTRATE Investigators*

From the Cleveland Clinic, Cleveland (S.E.N., S.J.N., E.M.T.); Montreal Heart Institute, Montreal (J.-C.T.); Pfizer, New London, CT (J.H.R., C.L.S., W.T.D.); Instytut Kardiologii, Warsaw, Poland (W.R.); Pinnacle Health at Harrisburg Hospital, Harrisburg, PA (W.B.B.); and Tchefuncte Cardiovascular Associates, Covington, LA (G.P.L.). Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

*Investigators and committees of the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.


ABSTRACT

BACKGROUND

Levels of high-density lipoprotein (HDL) cholesterol are inversely related to cardiovascular risk. Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, increases HDL cholesterol levels, but the functional effects associated with this mechanism remain uncertain.

METHODS

A total of 1188 patients with coronary disease underwent intravascular ultrasonography. After treatment with atorvastatin to reduce levels of low-density lipoprotein (LDL) cholesterol to less than 100 mg per deciliter (2.59 mmol per liter), patients were randomly assigned to receive either atorvastatin monotherapy or atorvastatin plus 60 mg of torcetrapib daily. After 24 months, disease progression was measured by repeated intravascular ultrasonography in 910 patients (77%).

RESULTS

After 24 months, as compared with atorvastatin monotherapy, the effect of torcetrapib–atorvastatin therapy was an approximate 61% relative increase in HDL cholesterol and a 20% relative decrease in LDL cholesterol, reaching a ratio of LDL cholesterol to HDL cholesterol of less than 1.0. Torcetrapib was also associated with an increase in systolic blood pressure of 4.6 mm Hg. The percent atheroma volume (the primary efficacy measure) increased by 0.19% in the atorvastatin-only group and by 0.12% in the torcetrapib–atorvastatin group (P=0.72). A secondary measure, the change in normalized atheroma volume, showed a small favorable effect for torcetrapib (P=0.02), but there was no significant difference in the change in atheroma volume for the most diseased vessel segment.

CONCLUSIONS

The CETP inhibitor torcetrapib was associated with a substantial increase in HDL cholesterol and decrease in LDL cholesterol. It was also associated with an increase in blood pressure, and there was no significant decrease in the progression of coronary atherosclerosis. The lack of efficacy may be related to the mechanism of action of this drug class or to molecule-specific adverse effects. (ClinicalTrials.gov number, NCT00134173.)
Epidemiologic studies demonstrate an inverse relationship between levels of high-density lipoprotein (HDL) cholesterol and the incidence of cardiovascular disease. Limited clinical trials have suggested that an increase in HDL cholesterol levels may reduce the progression of coronary atherosclerosis and decrease cardiovascular morbidity. Cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesteryl ester from HDL cholesterol to low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol. Recently, the administration of the CETP inhibitor torcetrapib has been shown to increase HDL cholesterol levels by more than 50%. However, the effectiveness of CETP inhibition as a strategy for antiatherosclerotic therapy has been controversial. Specific concern about the benefits and risks of torcetrapib emerged when initial clinical trials demonstrated a dose-dependent increase in blood pressure.

The development program for torcetrapib included three clinical trials of similar design, using coronary intravascular ultrasonography or carotid ultrasonography to determine whether partial inhibition of CETP with torcetrapib, administered with atorvastatin, would provide an additional antiatherosclerotic benefit, as compared with atorvastatin alone. After completion of these imaging trials but before the unblinding of the results, the data safety and monitoring board for a large torcetrapib clinical trial, called the Investigation of Lipid Level Management to Understand Its Impact on Atherosclerotic Events (ILLUMINATE) trial (NCT00134264), recommended that the study be terminated after an increase was observed in adverse cardiovascular events, including death from all causes. The sponsor promptly suspended the entire torcetrapib development program. We now report the results of the trial using intravascular ultrasonography as originally planned, with the additional use of these data to understand the mechanisms for adverse cardiovascular outcomes observed in the suspended torcetrapib trial.

Methods

Study Design

The Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial was a prospective, randomized, multicenter, double-blind clinical trial. The randomization was stratified according to geographic region (North America or Europe) and the dose of atorvastatin with the use of a permuted-block size of 4. The trial was designed by the Cleveland Clinic Cardiovascular Coordinating Center in collaboration with the sponsor. Institutional review boards at each study center approved the protocol, and patients provided written informed consent.

Patients between the ages of 18 and 75 years were eligible if they had undergone clinically indicated cardiac catheterization showing at least one stenosis on angiography with at least 20% narrowing and if the target vessel had less than 50% obstruction throughout a segment of 40 mm or longer. Patients were excluded from the study if the left main coronary artery had more than 50% obstruction, if the blood pressure was more than 140/90 mm Hg despite treatment, if the triglyceride level was more than 500 mg per deciliter (5.65 mmol per liter), or if the creatinine level was more than 1.7 times the upper limit of normal.

During a run-in phase of 4 to 10 weeks, patients were counseled on therapeutic lifestyle changes and administered atorvastatin (Lipitor, Pfizer) in an initial dose of 10 mg, which was subsequently titrated at 2-week intervals to 20 mg, 40 mg, or 80 mg, if needed, to achieve a level of LDL cholesterol within 15 mg per deciliter (0.39 mmol per liter) of 100 mg per deciliter (2.59 mmol per liter). Patients who met the LDL cholesterol goal were randomly assigned to receive either a fixed combination of atorvastatin (at the dose established during the run-in period) with 60 mg of torcetrapib or atorvastatin monotherapy with corresponding placebo tablets. A committee whose members were unaware of treatment assignment centrally adjudicated major cardiovascular adverse events.

The lead academic investigator wrote the manuscript and vouches for the accuracy and completeness of the data and the 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 rights to publish the results.

Intravascular Ultrasonography

After angiography, baseline intravascular ultrasound was performed. The methods used for image acquisition and measurement in regression–progression studies have been described previously. The results were screened for image...
quality in the core laboratory, and only patients whose findings met prespecified requirements for image quality were eligible for randomization. After 24 months, patients underwent a second intravascular ultrasonographic examination of the same coronary segment. Using digitized images, personnel who were unaware of patients’ clinical characteristics and treatment assignments performed manual planimetric measurements for cross sections spaced at 1.0-mm intervals. Measurements were performed in accordance with established standards. \[^16\] For each analyzed cross section, the operator measured the area of the external elastic membrane and the lumen. The accuracy and reproducibility of this method have been reported previously. \[^17\]

**Calculation of Efficacy Measures**

The primary efficacy measure, the change in percent atheroma volume, was calculated as follows:

$$\left( \frac{\sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \right) \times 100,$$

where EEM\text{}\text{CSA is the cross-sectional area of the external elastic membrane and LUMEN\text{}\text{CSA is the cross-sectional area of the lumen. The change in percent atheroma volume was calculated as the percent atheroma volume at 24 months minus the percent atheroma volume at baseline.**

A secondary measure of efficacy, normalized total atheroma volume, was also calculated. First, the average atheroma area per cross section was calculated as follows:

$$\frac{\sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{n},$$

where \(n\) is the number of cross sections in the pullback. To compensate for pullbacks of differing lengths, the total atheroma volume for each patient was calculated as the average atheroma area multiplied by the median number of cross sections for all patients in the study. The efficacy measure of the change in normalized total atheroma volume was calculated as the total atheroma volume at 24 months minus the total atheroma volume at baseline.

An additional secondary measure of efficacy, the change in atheroma volume in the most diseased 10-mm subsegment, was calculated by first determining the 10 contiguous cross sections with the greatest atheroma volume at baseline, then comparing the atheroma volume at follow-up for these cross sections.

**Statistical Analysis**

The trial database was transferred from the sponsor to the Cleveland Clinic, permitting independent confirmation of analyses. For continuous variables with a normal distribution, the mean (±SD) is reported. For variables not normally distributed, the median and interquartile ranges are reported. Measures of the efficacy of intravascular ultrasonography were adjusted with use of analysis of covariance. Lipoprotein levels are reported as the least-square mean (±SE) with the use of a linear model that included treatment group, geographic region, dose of atorvastatin, and baseline values. All reported P values are two-sided and not adjusted for multiple testing. For the primary efficacy measure (the change in percent atheroma volume), 413 patients in each study group were required for a power of 90% at a two-sided alpha of 0.05 to detect a treatment difference of 1.1% with a 5.0% standard deviation. Assuming a dropout rate of 25%, a total of 1100 patients were required.

**Patients**

From October 30, 2003, to August 16, 2004, at 137 centers in North America and Europe, 1188 patients were randomly assigned to study groups — 597 to the atorvastatin-only group and 591 to the torcetrapib–atorvastatin group. After 24 months of treatment, 910 patients (77%) remained in the study and had results on intravascular ultrasonography that could be evaluated at both baseline and follow-up. Of these patients, 446 were in the atorvastatin-only group and 464 in the torcetrapib–atorvastatin group. Demographic characteristics and the use of medications at baseline were similar in the two treatment groups (Table 1). The titrated dose of atorvastatin averaged 23 mg in both groups.

**Laboratory Results and Blood Pressure**

Table 1 summarizes laboratory values and blood pressure at baseline and during treatment for the 910 patients who completed the trial. After 24 months of treatment, HDL cholesterol levels in the atorvastatin-only group decreased from 45.2 to 43.9 mg per deciliter (1.17 to 1.14 mmol per liter), and levels of HDL cholesterol in the torcetrapib–atorvastatin group increased from 46.0 to 72.1 mg per deciliter (1.19 to 1.86 mmol per liter). After 24 months, LDL cholesterol levels in the atorvastatin-only group increased from 84.3 to 87.2 mg per deciliter (2.18 to 2.25 mmol per liter), and LDL...
cholesterol levels in the torcetrapib–atorvastatin group fell from 83.1 to 70.1 mg per deciliter (2.15 to 1.81 mmol per liter). Patients in the torcetrapib–atorvastatin group had a 61% relative increase in HDL cholesterol levels and a 20% relative decrease in LDL cholesterol levels, as compared with patients in the atorvastatin-only group. Baseline blood pressure was 120/73 mm Hg in both study groups. The average post-randomization systolic blood pressure increased by 2.0 mm Hg in the atorvastatin-only group and by 6.5 mm Hg in the torcetrapib–atorvastatin group, a least-square mean difference of 4.6 mm Hg (95% confidence interval [CI], 3.7 to 5.6; P<0.001). Median levels of high-sensitivity C-reactive protein were slightly higher in the torcetrapib–atorvastatin group at baseline (P=0.04) and at 24 months (P=0.02), but the change in C-reactive protein did not differ significantly between treatment groups (Table 1). Characteristics were similar in the 278 patients who did not complete the trial or undergo final intravascular ultrasonography.

**Intravascular Ultrasoundography**

Table 2 summarizes the change in the primary and secondary measures of efficacy, as measured by intravascular ultrasonography. The primary efficacy measure, the change in percent atheroma volume, increased by 0.19% in the atorvastatin-only group and by 0.12% in the torcetrapib–atorvastatin group (P=0.72). A secondary measure, normalized atheroma volume, showed a small favorable effect in the torcetrapib–atorvastatin group, a reduction of 9.5 mm³, as compared with a reduction of 6.3 mm³ in the atorvastatin-only group (P=0.02). The other secondary efficacy measure, the change in 10 mm of the most diseased segment, showed no statistical difference, with a reduction of 3.3 mm³ in the atorvastatin-only group and of 4.2 mm³ in the torcetrapib–atorvastatin group (P=0.12). There was no heterogeneity in the treatment difference for nearly all prespecified subgroups (see the Supplementary Appendix, which is available with the full text of this article at www.nejm.org). However, for patients whose percent atheroma volume was equal to or greater than the median value, there was a nearly significant effect in the torcetrapib–atorvastatin group (P=0.054). For patients with a baseline percent atheroma volume that was below the median value, the results showed a trend in favor of atorvastatin monotherapy (P=0.09). The interaction P value for this dichotomization was 0.005.

**Clinical Outcomes and Adverse Events**

Table 3 shows centrally adjudicated clinical events, blood-pressure–related adverse events, laboratory abnormalities, and reasons for study discontinuation. The frequency of major adverse cardiovascular events was similar in the two study groups. However, patients in the torcetrapib–atorvastatin group had more investigator-reported hypertensive adverse events (23.7% vs. 10.6%) and more blood-pressure values greater than 140/90 mm Hg (21.3% vs. 8.2%). A sustained increase of more than 15 mm Hg in systolic pressure occurred in 9.0% of patients in the torcetrapib–atorvastatin group and in 3.2% of patients in the atorvastatin-only group. Changes in systolic blood pressure for the two study groups are shown in Figure 1.

**Discussion**

A reduction in levels of LDL cholesterol represents the principal target for primary and secondary prevention of cardiovascular disease. However, many patients die or have complications from cardiovascular events despite the lowering of LDL cholesterol levels. Accordingly, research has focused on the development of agents that target other pathways in the pathogenesis of atherosclerosis. HDL cholesterol is an attractive target because epidemiologic evidence demonstrates a strong inverse relationship between HDL cholesterol levels and cardiovascular risk. The biologic plausibility of raising HDL cholesterol levels as a therapeutic strategy is further supported by evidence of the lipoprotein’s antiinflammatory properties, antioxidant effects, and ability to promote reverse cholesterol transport. Drugs that raise HDL cholesterol are available but have limitations. Fibric acid derivatives, such as gemfibrozil and fenofibrate, only modestly raise HDL cholesterol levels, generally by 7 to 15%. Large doses of niacin can raise HDL cholesterol levels by 25% or more, but administration is difficult in some patients because of the troublesome side effects of cutaneous flushing, occasional hepatotoxicity, and an increase in blood glucose levels.

Inhibition of CETP emerged as an attractive pharmaceutical target after studies involving Japanese patients with CETP deficiency showed very high HDL cholesterol levels. However, the potential value of this therapeutic strategy has generated considerable controversy. Our study provides evidence that directly addresses this controversy. After 24 months, treatment with the CETP inhibi-
Table 1. Baseline Characteristics, Blood Pressures, and Laboratory Values.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Only</th>
<th>Atorvastatin plus Torcetrapib</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>597</td>
<td>591</td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>57±9.2</td>
<td>56.9±9.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Male sex — %</td>
<td>70.5</td>
<td>70.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>30.3±5.2</td>
<td>30.6±6.2</td>
<td>0.41</td>
</tr>
<tr>
<td>History of diabetes — no. (%)</td>
<td>133 (22.3)</td>
<td>119 (20.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>History of hypertension — no. (%)</td>
<td>463 (77.6)</td>
<td>440 (74.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>112 (18.8)</td>
<td>102 (17.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Medication use at baseline — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>563 (94.3)</td>
<td>554 (93.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>457 (76.5)</td>
<td>449 (76.0)</td>
<td>0.82</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>392 (65.7)</td>
<td>392 (66.3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Statin</td>
<td>543 (91.0)</td>
<td>536 (90.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>Baseline values of patients who completed trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>446</td>
<td>464</td>
<td></td>
</tr>
<tr>
<td>Cholesterol — mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>157.5±27.1</td>
<td>157.7±27.6</td>
<td>0.91</td>
</tr>
<tr>
<td>LDL</td>
<td>84.3±18.9</td>
<td>83.1±19.7</td>
<td>0.35</td>
</tr>
<tr>
<td>HDL</td>
<td>45.2±11.2</td>
<td>46.0±12.8</td>
<td>0.34</td>
</tr>
<tr>
<td>Ratio of LDL cholesterol to HDL cholesterol</td>
<td></td>
<td></td>
<td>0.39‡</td>
</tr>
<tr>
<td>Median</td>
<td>1.90</td>
<td>1.88</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.6 to 2.2</td>
<td>1.5 to 2.3</td>
<td></td>
</tr>
<tr>
<td>Triglycerides — mg/dl</td>
<td></td>
<td></td>
<td>0.66‡</td>
</tr>
<tr>
<td>Median</td>
<td>123.9</td>
<td>122.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>89.0 to 170.0</td>
<td>88.5 to 179.0</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein — mg/liter</td>
<td></td>
<td></td>
<td>0.04‡</td>
</tr>
<tr>
<td>Median</td>
<td>1.8</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.9 to 3.4</td>
<td>1.1 to 4.3</td>
<td></td>
</tr>
<tr>
<td>Blood pressure — mm Hg§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>120.0±11.5</td>
<td>119.8±11.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73.4±7.4</td>
<td>73.3±7.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Follow-up at 24 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol — mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>157.2±31.2</td>
<td>167.5±37.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>87.2±22.6</td>
<td>70.1±25.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>43.9±12.1</td>
<td>72.1±24.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of LDL cholesterol to HDL cholesterol</td>
<td></td>
<td></td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.7 to 2.4</td>
<td>0.7 to 1.4</td>
<td></td>
</tr>
</tbody>
</table>
tor torcetrapib with atorvastatin increased HDL cholesterol levels by approximately 60% and lowered LDL cholesterol levels by 20%, as compared with atorvastatin monotherapy. After 24 months of treatment, HDL cholesterol levels were actually higher than LDL cholesterol levels in patients treated with torcetrapib. However, despite these favorable effects on lipoprotein levels, there was no significant reduction in the progression of coronary atherosclerosis according to percent atheroma volume, the primary efficacy measure (Table 2).

The results of torcetrapib administration can be considered in relation to the achieved LDL cholesterol levels. The mean on-treatment LDL cholesterol level has been a robust predictor of the progression rate of coronary atherosclerosis in trials involving the use of intravascular ultrasonography, showing regression when LDL cholesterol levels fall below approximately 75 mg per

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Only</th>
<th>Atorvastatin plus Torcetrapib</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides — mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>110.0</td>
<td>104.0</td>
<td>0.10‡</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>76.5 to 159.0</td>
<td>72.5 to 150.7</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein — mg/liter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
<td>1.8</td>
<td>0.02‡</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.7 to 3.0</td>
<td>0.8 to 4.2</td>
<td></td>
</tr>
<tr>
<td>Blood pressure — mm Hg§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122.0±10.1</td>
<td>126.4±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.3±6.4</td>
<td>76.0±6.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Change from baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol — %¶</td>
<td>Total</td>
<td>1.9±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>6.6±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>−2.2±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides — %</td>
<td>Median</td>
<td>−8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>−26.3 to 16.7</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein — mg/liter</td>
<td>Median</td>
<td>−0.2</td>
<td>0.19†</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>−1.0 to 0.5</td>
<td></td>
</tr>
<tr>
<td>Blood pressure — mm Hg§</td>
<td>Systolic</td>
<td>2.0±8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>0.8±5.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD unless otherwise indicated. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, LDL low-density lipoprotein, and HDL high-density lipoprotein.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Comparisons were performed with use of the Wilcoxon rank-sum test.
§ Values are the averages of all post-randomization measurements (586 patients in the torcetrapib–atorvastatin group and 589 in the atorvastatin-only group), including 1 patient who did not undergo final ultrasonography.
¶ Values are least-square means ±SE.
† P values were calculated from an analysis of covariance on rank-transformed data, with the last observation carried forward.
deciliter (1.94 mmol per liter) (Fig. 2). In our study, the atorvastatin-only group had a mean LDL cholesterol level of 87.2 mg per deciliter (2.25 mmol per liter), resulting in a net progression of 0.19%, which falls close to the expected result. Patients in the torcetrapib–atorvastatin group had a mean LDL cholesterol level of 70.1 mg per deciliter (1.81 mmol per liter), but the increase in percent atheroma volume was greater than would be expected (0.12%).

Estimating the benefits expected from a change in HDL cholesterol levels is more difficult. Although no trials involving intravascular ultrasonography have directly examined the effects of therapies to increase HDL cholesterol levels, a small study examined the effects of short-term infusions of an HDL-like agent, apolipoprotein A-I Milano, and showed significant regression, with a reduction in percent atheroma volume of 1.06%.10

A single secondary efficacy measure, the change in total atheroma volume, showed a favorable effect associated with torcetrapib. However, the treatment difference was relatively small (least-square mean, 3.2 mm³), particularly considering the long duration of the trial. Other studies using intravascular ultrasonography have shown larger treatment effects for therapies with a favorable effect on clinical outcomes. A trial comparing moderate versus intensive statin therapy showed a treatment difference for total atheroma volume of 5.5 mm³ after 18 months.11 A more recent study using very intensive statin therapy for 24 months resulted in a regression of 14.7 mm³ in total atheroma volume.14 The infusion of apolipoprotein A-I Milano reduced total atheroma volume by 14.1 mm³. Accordingly, the totality of the data, with no benefit observed for the primary end point and one secondary end point and a small favorable effect for another secondary end point, supports the conclusion that the lipoprotein effects of torcetrapib failed to provide the anticipated antiatherosclerotic benefits. Accordingly, it seems likely that other drug effects prevented the slowing of atherosclerosis expected from the seemingly favorable lipid-modulating benefits of torcetrapib.

Several potential mechanisms could explain the lack of antiatherosclerotic efficacy observed in the torcetrapib–atorvastatin group. The increase in systolic blood pressure observed in this group averaged 4.6 mm Hg, with 21.3% of patients exceeding 140/90 mm Hg and 9.0% having a sustained increase of more than 15 mm Hg (Fig. 1). These increases in blood pressure may have counterbalanced any benefits derived from the increases in HDL cholesterol levels and decreases in LDL cholesterol levels. Previous trials using intravascular ultrasonography have shown a relationship between a change in blood pressure and the progression of atherosclerosis.12,26 The administration of amlodipine for 24 months lowered systolic blood pressure by 4.9 mm Hg and reduced percent atheroma volume by 0.8%, as compared with placebo.12 Accordingly, it seems plausible that a mean increase in blood pressure of 4.6 mm Hg in the torcetrapib–atorvastatin group (as compared with the atorvastatin-only group) might increase percent atheroma volume by a similar amount (0.8%).

The possibility that the HDL cholesterol produced by torcetrapib might be dysfunctional also deserves careful consideration. There are conflicting data on the prevalence of atherosclerosis in patients with CETP deficiency or genetic polymorphisms. Some studies show protection, whereas others show increased susceptibility to atherosclerotic disease.27 Proponents of CETP inhibition have proposed that the complete absence of this enzyme and associated abnormalities in homozygotes might produce dysfunctional HDL cholesterol, whereas partial inhibition would yield functional HDL particles.7,28 In transgenic animal models of atherosclerosis, CETP inhibition has produced mixed results, with both proatherogenic and antiatherogenic effects, depending on the species studied.5 Studies showing a proatherogenic effect were often performed in animals that do not naturally express CETP. In cholesterol-fed rabbits that express CETP, torcetrapib provided protection against the development of aortic atherosclerosis.29

The functionality of HDL cholesterol produced through CETP inhibition remains uncertain. Figure 3 illustrates the metabolism of HDL cholesterol, its role in reverse cholesterol transport, and the expected effects of CETP inhibition. Lipid-poor apolipoprotein A-I circulates as a discoidal particle, which is the preferred acceptor of cholesterol effluxed from macrophages through the
Table 2. Primary and Secondary Study End Points as Evaluated on Intravascular Ultrasonography at Baseline and at 24-Month Follow-up with Changes from Baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Only (N = 446)</th>
<th>Atorvastatin plus Torcetrapib (N = 464)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent atheroma volume*</td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>37.1±8.5</td>
<td>37.0±8.6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>36.5</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>31.2–42.7</td>
<td>31.3–42.8</td>
<td></td>
</tr>
<tr>
<td>Normalized total atheroma volume (mm$^3$)†</td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>198.7±86.2</td>
<td>196.1±90.8</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>185.1</td>
<td>177.3</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>134.8–252.2</td>
<td>133.9–238.2</td>
<td></td>
</tr>
<tr>
<td>Atheroma volume of most diseased 10-mm segment (mm$^3$)†</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>58.2±25.7</td>
<td>56.8±28.7</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55.8</td>
<td>54.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>(39.5–74.2)</td>
<td>(35.9–72.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up at 24 months</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Percent atheroma volume</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>37.3±8.8</td>
<td>37.1±8.6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>36.3</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>31.1–43.4</td>
<td>31.4–42.7</td>
<td></td>
</tr>
<tr>
<td>Normalized total atheroma volume (mm$^3$)</td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>192.4±85.7</td>
<td>186.7±87.6</td>
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<tr>
<td>Median</td>
<td>176.4</td>
<td>169.7</td>
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<tr>
<td>Interquartile range</td>
<td>129.2–242.8</td>
<td>127.3–226.5</td>
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<tr>
<td>Atheroma volume of most diseased 10-mm segment (mm$^3$)</td>
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<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>54.9±24.7</td>
<td>52.7±26.5</td>
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</tr>
<tr>
<td>Median</td>
<td>53.4</td>
<td>50.5</td>
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</tr>
<tr>
<td>Interquartile range</td>
<td>37.4–69.7</td>
<td>34.5–65.3</td>
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</tr>
<tr>
<td><strong>Change from baseline</strong></td>
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<td></td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>0.19±2.83</td>
<td>0.12±2.99</td>
<td></td>
</tr>
<tr>
<td>Least-square mean ±SE</td>
<td>0.19±0.14</td>
<td>0.12±0.13</td>
<td></td>
</tr>
<tr>
<td>Normalized total atheroma volume (mm$^3$)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>−6.3±22.2</td>
<td>−9.4±21.0</td>
<td></td>
</tr>
<tr>
<td>Least-square mean ±SE</td>
<td>−6.3±1.0</td>
<td>−9.5±1.0</td>
<td></td>
</tr>
<tr>
<td>Atheroma volume of most diseased 10-mm segment (mm$^3$)</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>−3.3±9.1</td>
<td>−4.1±8.6</td>
<td></td>
</tr>
<tr>
<td>Least-square mean ±SE</td>
<td>−3.3±0.4</td>
<td>−4.2±0.4</td>
<td></td>
</tr>
</tbody>
</table>

* This variable was the primary efficacy measure.
† This variable was a secondary efficacy measure.
### Table 3. Adverse Events, Clinical End Points, and Reasons for Discontinuation.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin Only (N = 597)</th>
<th>Atorvastatin plus Torcetrapib (N = 591)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular event†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>6 (1.0)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>16 (2.7)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>8 (1.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>34 (5.7)</td>
<td>47 (8.0)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>95 (15.9)</td>
<td>114 (19.3)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>13 (2.2)</td>
<td>10 (1.7)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>4 (0.7)</td>
<td>9 (1.5)</td>
</tr>
<tr>
<td>Composite of death from coronary heart disease, nonfatal myocardial</td>
<td>57 (9.5)</td>
<td>62 (10.5)</td>
</tr>
<tr>
<td>infarction, nonfatal stroke, and hospitalization for unstable angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of death from coronary heart disease, nonfatal myocardial</td>
<td>117 (19.6)</td>
<td>124 (21.0)</td>
</tr>
<tr>
<td>infarction, nonfatal stroke, hospitalization for unstable angina, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>coronary revascularization</td>
<td></td>
<td></td>
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<tr>
<td><strong>Blood pressure–related event</strong></td>
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<td></td>
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<tr>
<td>Investigator-reported hypertensive adverse event</td>
<td>63 (10.6)</td>
<td>140 (23.7)</td>
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<tr>
<td>Blood pressure &gt;140/90 mm Hg</td>
<td>49 (8.2)</td>
<td>126 (21.3)</td>
</tr>
<tr>
<td>Blood pressure increase &gt;15 mm Hg</td>
<td>19 (3.2)</td>
<td>53 (9.0)</td>
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<tr>
<td><strong>Abnormality in laboratory value</strong></td>
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<td></td>
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<tr>
<td>Aspartate aminotransferase &gt;3× ULN</td>
<td>2 (0.3)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;3× ULN</td>
<td>5 (0.8)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5× ULN</td>
<td>4 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>&gt;10× ULN</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>140</td>
<td>135</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preference of patient</td>
<td>57</td>
<td>48</td>
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<tr>
<td>Adverse event</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>6‡</td>
</tr>
<tr>
<td>Unspecified</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

* ULN denotes upper limit of normal.  
† Data on adverse events for each patient were collected for 28 days after the administration of the last dose of study medication and were adjudicated by a central committee. The results exclude three events that remain to be adjudicated.  
‡ Number includes an additional patient who died after completing the study.
transmembrane ATP-binding cassette transporter A1 (ABCA1). CETP inhibition, however, increases the concentration of mature, cholesterol-laden alpha HDL particles, which are not optimal acceptors of ABCA1-mediated efflux, although they may facilitate reverse cholesterol transport mediated by ATP-binding cassette transporter G1 (ABCG1) or scavenger receptor class B1 (SR-B1) (Fig. 3). Recent evidence suggests that in vivo modification of HDL cholesterol can result in an abnormal particle with proinflammatory, proatherogenic properties.30,31

It is also possible that toxic effects unique to the torcetrapib molecule may have adversely affected the progression rate. The increase in blood pressure observed in torcetrapib-treated patients may reflect more generalized vascular toxicity, effects that could have counterbalanced any antiatherosclerotic benefits derived from an increase in HDL cholesterol. In our study, a greater number of adverse cardiovascular events were observed in the torcetrapib—atorvastatin group than in the atorvastatin-only group (Table 3). Although these differences were not statistically significant, the study was not powered to evaluate cardiovascular outcomes. These results are consistent with the observation of worse clinical outcomes among patients who received torcetrapib in the prematurely terminated morbidity–mortality trial.

The possibility must be considered that CETP inhibition, regardless of specific molecular toxicity, will not provide antiatherosclerotic benefits. A critical question is whether the failure of torcetrapib precludes the possibility that other drugs in this class might be successfully developed as effective antiatherosclerotic agents. It is difficult to determine the extent to which the failure of torcetrapib was the result of dysfunctional HDL cholesterol, properties that increased blood pressure, or other toxic effects specific to this agent. Other CETP inhibitors do not appear to have a pressor effect.32 Future post hoc analyses from our study and other torcetrapib trials will attempt to elucidate the effect of changes in HDL cholesterol, LDL cholesterol, and blood pressure on trial results. Given the potential importance of developing therapies to raise HDL cholesterol levels, it would seem imprudent to abandon studies of CETP inhibition because of the failure of  

![Figure 1. Changes in Systolic Blood Pressure in the Two Study Groups.](image1)

The graph shows data for all patients for whom blood pressure measurements were available — 586 in the atorvastatin-only group and 589 in the atorvastatin—torcetrapib group — regardless of whether the patients underwent final intravascular ultrasonography.

![Figure 2. Relationship between the Change in Percent Atheroma Volume and LDL Cholesterol in Regression–Progression Trials Using Intravascular Ultrasonography.](image2)

Values for percent atheroma volume represent the prespecified measures in the cited studies: mean values, medians, or least-square means. ILLUSTRATE denotes Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ClinicalTrials.gov number, NCT00134173), REVERSAL the Reversal of Atherosclerosis with Aggressive Lipid Lowering,11 CAMELOT Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis,12 A-PLUS Avasimibe and Progression of Lesions on Ultrasound,23 ACTIVATE the A-PLUS Acute Coronary Syndrome Trial: Effect of Avasimibe on Plaque Progression (ClinicalTrials.gov number, NCT00295313), and ASTEROID A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden24 (NCT00240318).
a single agent in the class, particularly an agent with adverse effects on blood pressure.

The results of our study also have important implications for the use of imaging methods in the development of novel antiatherosclerotic therapies. Intravascular ultrasonography has been increasingly proposed as one of several imaging methods for determining the potential of new agents. Our results would have predicted neither benefit nor harm from the administration of torcetrapib. Although this finding may appear to be incongruent with the failed clinical out-

---

**Figure 3. Schematic Representation of the Metabolism of HDL Cholesterol.**
Apolipoprotein A-I (ApoA-I) is secreted by the liver as a discoidal particle containing protein and phospholipid. This lipid-poor protein interacts with ATP-binding cassette transporter A1 (ABCA1) in macrophages, removing intracellular free cholesterol. When these lipid-poor HDL particles accept additional cholesterol, they mature into larger, spheroidal particles that do not actively interact with the ABCA1 transporter. However, the mature HDL particle can participate in reverse cholesterol transport through uptake in the liver by the scavenger receptor class B1 (SR-B1), potentially regenerating lipid-poor discoidal HDL cholesterol. Alternatively, mature HDL particles can also accept additional free cholesterol through the ATP-binding cassette transporter G1 (ABCG1). Mature HDL particles can also efflux free cholesterol from macrophages through the SR-B1 receptor. Cholesteryl ester transfer protein (CETP) inhibitors increase concentrations of the larger, mature alpha-HDL particles by blocking transfer of cholesteryl ester to particles of very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol. Pathways shown in blue represent the potentially beneficial effects of CETP inhibition, those shown in green may remain relatively unaffected, and those shown with dashed lines have potentially reduced activity after CETP inhibition. FC denotes free cholesterol, PL phospholipids, CE cholesteryl ester, and LPL lipoprotein lipase.
comes trial for torcetrapib, intravascular ultrasonography and other imaging techniques would not be sensitive to detect nonatherosclerotic vascular toxicity or other safety problems with any new drug. It is reassuring that even in the absence of a failed clinical outcomes trial for torcetrapib, our study would not have supported regulatory approval. Ultimately, any novel antiatherosclerotic therapy must demonstrate favorable results in clinical events trials, and atherosclerosis imaging will probably not replace the need for such outcomes studies. However, our results support the cautious use of intravascular ultrasonography and other imaging methods in the initial assessment of new antiatherosclerotic agents to select candidate therapies for large-scale clinical trials.

Finally, our findings demonstrate the great difficulty in developing therapies to interrupt the atherosclerotic disease process. Twenty years after the introduction of statins, we are still waiting for the next breakthrough.

Supported by Pfizer.

Dr. Nissen reports receiving research support, through the Cleveland Clinic Cardiovascular Coordinating Center, to perform clinical trials from Pfizer, AstraZeneca, Sankyo, Takeda, Sanofi-Aventis, and Eli Lilly. Dr. Nissen reports consulting for many pharmaceutical companies, but all honoraria or consulting fees are donated directly to charity so that he receives neither income nor a tax deduction. Dr. Tardif reports holding the Pfizer and Canadian Institutes of Health Research chair in atherosclerosis and receiving consulting fees from Pfizer and AstraZeneca; Dr. Nicholls, receiving honoraria from Pfizer, AstraZeneca, and Merck Schering-Plough, consulting fees from AstraZeneca and Anthera Pharmaceuticals, and research support from Lipid Sciences; Dres. Revkin, Shear, and Duggan, being employees of Pfizer and owning Pfizer stock; and Dr. Tuzcu, receiving consulting fees from Pfizer and honoraria from Pfizer and Merck. No other potential conflict of interest relevant to this article was reported.

We thank D. Brennan, K. Wolski, N. Juran, E. McErlean, M. Goormastic, L. Gennotti, W. Davidson, M. Ennis, K. Burnside, A. Chin, M. Li, and A. O’Reilly.

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Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis


ABSTRACT

BACKGROUND

Idiopathic pulmonary fibrosis is progressive and often fatal; causes of familial clustering of the disease are unknown. Germ-line mutations in the genes \textit{hTERT} and \textit{hTR}, encoding telomerase reverse transcriptase and telomerase RNA, respectively, cause autosomal dominant dyskeratosis congenita, a rare hereditary disorder associated with premature death from aplastic anemia and pulmonary fibrosis.

METHODS

To test the hypothesis that familial idiopathic pulmonary fibrosis may be caused by short telomeres, we screened 73 probands from the Vanderbilt Familial Pulmonary Fibrosis Registry for mutations in \textit{hTERT} and \textit{hTR}.

RESULTS

Six probands (8%) had heterozygous mutations in \textit{hTERT} or \textit{hTR}; mutant telomerase resulted in short telomeres. Asymptomatic subjects with mutant telomerase also had short telomeres, suggesting that they may be at risk for the disease. We did not identify any of the classic features of dyskeratosis congenita in five of the six families.

CONCLUSIONS

Mutations in the genes encoding telomerase components can appear as familial idiopathic pulmonary fibrosis. Our findings support the idea that pathways leading to telomere shortening are involved in the pathogenesis of this disease.
DIOPATHIC PULMONARY FIBROSIS HAS A predictable, progressive clinical course that ultimately leads to respiratory failure. Irreversible fibrosis is the hallmark of the disease, which has a characteristic radiographic appearance most often associated with the pathological lesion of usual interstitial pneumonia. Although both genetic and environmental factors have been implicated, the cause of idiopathic pulmonary fibrosis is unknown—as, indeed, its name implies. Treatment approaches that target the immune system have not proved to be successful.1 From 2 to 20% of patients with idiopathic pulmonary fibrosis have a family history of the disease; inheritance appears to be autosomal dominant with variable penetrance.1–3 Aside from one large kindred with a mutation in the gene encoding surfactant protein C in affected family members, the genetic basis of familial forms of idiopathic pulmonary fibrosis is not understood.4

Telomerase is a specialized polymerase that adds telomere repeats to the ends of chromosomes.5 It has two essential components: a catalytic component, telomerase reverse transcriptase (hTERT), and an RNA component (hTR); the latter provides the template for nucleotide addition by hTERT.6–8 The addition of telomeric repeats (a repeat comprising the six nucleotides — TTAGGG — complementary to the template in hTR) onto the ends of the chromosome partly offsets the shortening that occurs during DNA replication. Telomeres shorten with each cell division and ultimately activate a DNA damage response that leads to apoptosis or cell-cycle arrest.9–13 Telomere length thus limits the replicative capacity of tissues and has been implicated in age-related disease.9–11,14,15

Dyskeratosis congenita is a rare hereditary disorder initially described on the basis of a triad of mucocutaneous manifestations: skin hyperpigmentation, oral leukoplakia, and nail dystrophy.16 The most common cause of death in patients with dyskeratosis congenita is bone marrow failure due to aplastic anemia. Pulmonary disease is present in 20% of patients and is the second most common cause of death.16–18 The X-linked form of dyskeratosis congenita is severe and associated with mutations in the DKC1 gene.19 Autosomal dominant cases of dyskeratosis congenita are rare, can present later in adulthood, and often lack the classic skin manifestations. In some families, the hematopoietic defects develop first, implying that despite the originally given name, the dyskeratosis is not canonical.20 Heterozygous mutations in hTR and hTERT, the essential components of telomerase, underlie the genetic defect in families with dominant inheritance, indicating that half the usual dose of telomerase is inadequate for telomere maintenance, and tissues of high turnover, such as the bone marrow, are susceptible.21–24 In autosomal dominant dyskeratosis congenita, anticipation can be seen in which phenotypes present earlier and more severely in successive generations.21,24,25 This pattern implies that in these patients, it is not the telomerase mutation itself but the short telomeres that determine the severity of the disease.14,24,26

We recently identified a pedigree with autosomal dominant dyskeratosis congenita that carried a null hTERT allele but lacked the typical mucocutaneous features.24 In this kindred, pulmonary fibrosis was dominantly transmitted and was the only manifestation of disease in one mutation carrier. The clinical presentation and pattern of fibrosis in this subject were typical of the idiopathic form of the disease. Since familial idiopathic pulmonary fibrosis is also dominantly inherited, we hypothesized that telomere shortening causes this disease and that mutations in telomerase may contribute to it.

METHODS

SUBJECTS

Subjects and their families were recruited into the Vanderbilt Familial Pulmonary Fibrosis Registry on the basis of the presence of two or more cases of idiopathic pulmonary fibrosis. (We did not limit families to those in which only first-degree relatives were affected.) Subjects were excluded from the study if they had a secondary cause of pulmonary fibrosis or if they had skin manifestations suggestive of dyskeratosis congenita. Subjects were recruited from the Vanderbilt Idiopathic Pulmonary Fibrosis Clinic or were referred from other sites in North America between 1996 and 2004. The study was approved by the local institutional review boards, and written informed consent was obtained from all subjects. Diagnostic confirmation was based on a detailed clinical assessment (Table 1, and Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). We used the consensus classification of idiopathic interstitial pneumonia in individual cases.27 At the time the
registry was accessed, all 73 probands were reported by their clinicians to be North Americans of European descent.

**SEQUENCE ANALYSIS**

Genomic DNA was isolated from peripheral blood with the use of standard methods. We amplified and sequenced hTR in both directions, as described previously.\(^{21}\) We amplified and sequenced the 16 exons of hTERT and its 3’ untranslated region with the use of primers listed in Table 2 of the Supplementary Appendix. Amplicons of hTERT were sequenced in one direction, and suspected changes were confirmed in the opposite strand. Mutations in the probands and their relatives were confirmed by bidirectional sequencing. Sequences were inspected manually with the use of Sequencher software, and variants were compared with public databases. Coding and noncoding variants are listed in Table 3 of the Supplementary Appendix.

**TELOMERES AND TELOMERASE**

A reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay was performed with the use of RNA isolated from peripheral blood to make complementary DNA (cDNA). Primers were designed to span exons where a mutation was predicted to alter splicing; primer sequences are available on request. PCR products were cloned, and the sequence was verified.

The average length of telomeres was measured in peripheral-blood lymphocytes by flow fluorescence in situ hybridization (FISH), as described previously.\(^{28}\)

Point mutations were generated, and the telomerase complex was reconstituted in vitro.\(^{24}\) Telomerase activity was assayed without amplification, with the use of a modified direct assay.\(^{29,30}\)

### RESULTS

**MUTATIONS AFFECTING TELOMERASE COMPONENTS**

Of 73 probands who were screened, 6 (8%) had heterozygous mutations in hTERT or hTR. Five probands had mutations in hTERT (two missense, two splice junction, and one frameshift), and one proband had a mutation in hTR (Table 1, and Fig. 1 of the Supplementary Appendix). None of the hTERT mutations were present in 623 unaffected subjects, as determined in other studies.\(^{23,31}\)

Of these subjects, 140 described themselves as white, with the rest describing themselves as black,

<table>
<thead>
<tr>
<th>Proband No.</th>
<th>Mutation</th>
<th>Sex</th>
<th>Age at Onset of Study</th>
<th>Presenting Symptom</th>
<th>Smoking History</th>
<th>At Time of Study</th>
<th>Pulmonary Function</th>
<th>Findings on Lung Biopsy</th>
<th>Complete Blood Count</th>
<th>Telomerase Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AII.1</td>
<td>hTERT</td>
<td>M</td>
<td>77</td>
<td>Dyspnea</td>
<td>None</td>
<td>4.45 (68)</td>
<td>3.02 (68)</td>
<td>14.2 (76)</td>
<td>Usual interstitial pneumonia</td>
<td>5,500 14.0 206,000</td>
</tr>
<tr>
<td>BIII.5</td>
<td>hTERT</td>
<td>M</td>
<td>58</td>
<td>Cough</td>
<td>None</td>
<td>3.17 (44)</td>
<td>2.10 (44)</td>
<td>11.5 (49)</td>
<td>Usual interstitial pneumonia</td>
<td>8,800 14.1 282,000</td>
</tr>
<tr>
<td>CII.7</td>
<td>hTERT</td>
<td>M</td>
<td>58</td>
<td>Dyspnea</td>
<td>30 pack-years</td>
<td>5.28 (69)</td>
<td>3.55 (66)</td>
<td>12.8 (47)</td>
<td>Usual interstitial pneumonia</td>
<td>8,800 16.2 201,000</td>
</tr>
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<td>DIII.2</td>
<td>hTERT</td>
<td>F</td>
<td>48</td>
<td>Dyspnea</td>
<td>32 pack-years</td>
<td>3.25 (68)</td>
<td>NA</td>
<td>1.31 (43)</td>
<td>NA</td>
<td>6,800 12.8 218,000</td>
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<td>1.69 (47)</td>
<td>12.5 (54)</td>
<td>Usual interstitial pneumonia</td>
<td>10,800 13.8 317,000</td>
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<tr>
<td>FIII.5</td>
<td>hTR</td>
<td>F</td>
<td>60</td>
<td>Dyspnea</td>
<td>66‡</td>
<td>2.48 (51)</td>
<td>1.2 (45)</td>
<td>7.07 (32)</td>
<td>Usual interstitial pneumonia</td>
<td>2.48 (51) 7.07 (32)</td>
</tr>
</tbody>
</table>

*Identifiers for all probands refer to subjects shown in Figure 1. TLC denotes total lung capacity, FVC forced vital capacity, DLCO carbon monoxide diffusing capacity, WBC white cells, Hgb hemoglobin, IVS intervening sequence between exons (intronic), and NA not available.

† The age at the time of death is shown.
Figure 1. Pedigrees of Six Probands with Telomerase Mutations.

Arrows point to the proband in each family, and bold italic numbers indicate subjects for whom DNA was available for sequencing. Subjects in whom telomere length was measured are indicated by asterisks. Mutation status is indicated by the symbols shown in the key, with squares indicating male sex and circles indicating female sex. Deceased family members are indicated by slashes through the symbols. In Family D, Subject DII.1 is an obligate carrier, given that two of his children carry the mutation and the mother does not. A total of 19 subjects with confirmed idiopathic pulmonary fibrosis are included among the six families shown. The seven asymptomatic carriers in younger generations were on average 11 years younger than the probands at the time of diagnosis: 40, 44, 46, 50, 52, 55, and 68 years of age. In Family F, three subjects had aplastic anemia, and Subject FIII.16 died from acute myeloid leukemia, probably in the setting of aplastic anemia. IPF denotes idiopathic pulmonary fibrosis.
Hispanic, or Asian. The hTR mutation was also absent in 194 healthy controls. Of these subjects, 123 described themselves as white, with the remaining subjects describing themselves as black, Hispanic, or Asian.22

**Mutations Associated with Disease and Short Telomeres**

To determine whether telomerase mutations segregated with idiopathic pulmonary fibrosis in families, we examined the pedigrees. The pattern of inheritance was consistent with autosomal dominant inheritance of the disease (Fig. 1). The mutant allele was present in affected subjects and was generally absent in asymptomatic subjects of the same generation. We identified mutation carriers who did not have symptoms of the disease. These subjects were on average 11 years younger than the probands at the time of diagnosis (Fig. 1). This observation is consistent with the variable penetrance associated with familial idiopathic pulmonary fibrosis and also suggests that the onset of disease may be age dependent.

To assess whether mutant telomerase is associated with short telomeres, we measured the telomere length in lymphocytes. The average telomere length was significantly less in the probands and asymptomatic mutation carriers than in their relatives who did not carry the mutation (P = 0.006) (Fig. 2A). A comparison of the telomere length in mutation carriers with that in 400 healthy controls, according to age,23 showed that mutation carriers fell below the 10th percentile of the controls (P = 0.018), whereas their relatives who were noncarriers clustered near the median (P = 0.575) (Fig. 2B). Mutant telomerase was therefore associated with short telomeres.

**Impaired Activity of Mutant Telomerase**

We next examined the consequences of hTERT and hTR mutations on telomerase function. We first examined the two missense mutations in hTERT, glutamine replacing leucine at residue 55 (Leu55Gln) and methionine replacing threonine at residue 1110 (Thr1110Met). The Leu55Gln substitution identified in the proband of Family A is in a highly conserved region of the N-terminal; an amino acid substitution of Leu55 may alter telomerase activity.
merase RNA binding and thus the catalytic efficiency of telomerase. The Thr1110 residue is also highly conserved and lies in the C-terminal domain of hTERT, a domain that is thought to mediate recruitment of telomerase to the telomere. Both mutant versions of hTERT (Leu55Gln and Thr1110Met) had impaired activity, as compared with the wild-type enzyme (Fig. 3C and 3D). Since heterozygous mutations sometimes interfere with the function of the wild-type allele, we assayed the telomerase activity of a mixture of wild-type and mutant versions of the enzyme and observed no dominant negative effect (data not shown).

We also examined the effect of the hTR 98 G→A substitution (observed in the proband of Family F) on telomerase activity. This mutation is predicted to impair base pairing in a helix in the essential pseudoknot domain of hTR. Moreover, since 98G is conserved in telomerase RNA in all vertebrates, a mutation at this site is expected to alter activity. When telomerase was reconstituted with the mutant hTR 98A allele, activity was severely impaired (Fig. 3C and 3D).

We next examined the potential consequences of the three mutations in hTERT. The deletion of nucleotide C at codon 112 in the proband of Family C leads to a frameshift mutation and is predicted to result in a nonfunctional, truncated protein. Both splice-junction mutations in Family B and Family D occur at consensus sequences that are conserved in 99.9% of all eukaryotic genes and are therefore predicted to alter splicing. We examined the cDNA of primary cells from a subject in Family D who carried the IVS9-2 A→C mutation, indicating that the heterozygous mutation at this consensus splice junction leads to the skipping of exon 10 but retention of the reading frame (Fig. 3E). According to these findings, obtained by RT-PCR, synthesis of a protein of nearly full length is predicted. However, this mutant TERT is predicted to lack an essential motif (the C motif) in the reverse-transcriptase domain and thus to result in a functionally null protein (Fig. 3A).

**CLINICAL REVIEW**

We reexamined the probands for the most common features of dyskeratosis congenita. None of the probands had cytopenias (Table 1), and none had any of the classic features of dyskeratosis congenita at the time of diagnosis. To discern whether these six families had hidden cases of dyskeratosis congenita, we queried family members and medical records for evidence of aplastic anemia. We identified no cases of aplastic anemia in five of the six families. In Family F, we identified three subjects with aplastic anemia and a fourth subject with probable aplastic anemia (Fig. 1). In this family, subjects with a hematopoietic defect died at a younger age (25, 26, 31, and 81 years, with a mean of 41 years) than did those with idiopathic pulmonary fibrosis (76, 70, 63, 57, 60, and 66 years, with a mean of 65 years). We also explored the possibility that asymptomatic mutation carriers with short telomeres had cytopenias that reflected early changes of aplastic anemia. We examined complete blood counts in members of five of the families — Family A, Family B, Family C, Family D, and Family E — and found no abnormalities.

To assess whether the pulmonary fibrosis in the probands could be differentiated from other cases of idiopathic pulmonary fibrosis, we reviewed the clinical data. The presentation, age at onset, and findings on computed tomography were indistinguishable from those of other cases of the disease (Table 1 and Fig. 4). None of these subjects had a response to trials of immunosuppressive therapy. In all cases, the proband had

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**Figure 3 (facing page). Biochemical Consequences of Telomerase Mutations in Probands.**

Panel A shows conserved domains of hTERT with missense mutations, as indicated. Colors indicate conserved domains in hTERT shared with other reverse transcriptases. The Leu55Gln mutation lies in the telomerase essential N-terminal (TEN) domain, and Thr1110Met is in one of four conserved C-terminal domains. Panel B shows the secondary structure of hTR, with the site of the mutation indicated by an asterisk. The 98 G→A substitution lies in a critical helix of the pseudoknot domain, which contains the telomere template and is responsible for binding to TERT. Panel C shows the telomerase activity of mutant hTERT and hTR alleles, as measured by the direct assay and the intensity and pattern of the repetitive ladder. Panel D shows the quantitation of telomerase activity at the second major band, as indicated by the arrowhead in Panel C. Mean activity was calculated on the basis of three to five experiments; the I bars represent standard errors. Panel E shows the results of an RT-PCR assay across exons 9 through 11 from a subject with an hTERT 9-2 A→C mutation, indicating that the heterozygous mutation at this consensus splice junction leads to the skipping of exon 10. As a result, the mutant TERT lacks the essential motif C of the reverse-transcriptase domain.
undergone lung biopsy, and five of the six probands had the common lesion of usual interstitial pneumonia. A biopsy specimen obtained from the sixth proband showed idiopathic interstitial pneumonia, not classifiable. Different idiopathic interstitial pneumonia pathological lesions have been described in the same patient, as well as in members of the same family with the disease, underscoring the need for precise molecular characterization.4,35
Figure 4. High-Resolution Computed Tomographic Images of the Midlung (Panel A through Panel D) and Bases (Panel E through Panel H) in Probands in Four Families.

Subject numbers are shown in the upper right-hand corners of the panels. In all four probands, subpleural honeycombing and increased reticular densities are visible in the views at the bases. These changes extend up to the midlung and apexes in some subjects with more advanced stages of disease (e.g., Subject DIII.2).

DISCUSSION

We have shown that mutant telomerase is associated with familial idiopathic pulmonary fibrosis, which suggests that the spectrum of disease caused by telomere shortening is more extensive than previously appreciated and that a subgroup of families with pulmonary fibrosis falls on that spectrum.

Short dysfunctional telomeres activate a DNA damage response that leads to cell death or cell-cycle arrest. This response is manifested clinically as organ failure in tissues of high turnover (bone marrow, skin, and gastrointestinal tract) in patients with, and in an animal model of, dyskeratosis congenita. The presence of pulmonary fibrosis in dyskeratosis congenita, along with the presence of telomerase mutations in some families with idiopathic pulmonary fibrosis, suggests that bronchoalveolar epithelium is also constantly replaced and relies on local progenitor reserves that are limited by short telomeres.

On the basis of these findings, we propose that the fibrotic lesion in patients with short telomeres is provoked by a loss of alveolar cells rather than by a primary fibrogenic process, such as one that would seem to occur in autoimmune disease associated with lung fibrosis. This view is supported by the fact that misfolded surfactant protein C (present in affected subjects carrying a mutation in the corresponding gene) appears to be toxic to alveolar cells. Therefore, it is possible that in some types of fibrosis, damage of epithelial cells leads to a remodeling response that appears clinically as usual interstitial pneumonia. Taken together, these considerations may explain the lack of success in reversing idiopathic fibrosis with agents that modulate immune or inflammatory signals and support the idea that at least in some cases, strategies aimed at preventing the loss of alveolar cells, or local responses to such cell loss, may have a greater clinical impact.

Although mutations in the essential components of telomerase do not seem to account for a majority of cases of familial pulmonary fibrosis, telomere shortening as a process may still contribute to the pathogenesis. There is evidence that short telomeres, rather than telomerase mutations, correlate with disease in dyskeratosis congenita. In an animal model of dyskeratosis congenita, wild-type mice who inherit short telomeres appear to have an occult genetic disease and display phenotypes similar to those in mice that are heterozygous for mutant telomerase RNA. Acquired states that increase tissue turnover are also associated with short telomeres. One study showed that both current and former smokers had shorter telomeres than did age-matched nonsmokers. In addition, there is some evidence that telomeres of the alveolar epithelium in smokers are shorter than those of the alveolar
epithelium in nonsmokers.37 It is therefore possible that somatic telomere shortening, caused by conditions that increase cell turnover (e.g., smoking), could contribute to fibrosis. In a study evaluating disease onset in relatives of familial probands with idiopathic pulmonary fibrosis, cigarette smoking and older age were the strongest predictors.35 Because telomere shortening occurs with aging and can be acquired, it may contribute to the disease pathogenesis even in persons with wild-type telomerase.

Our study will have clinical implications, assuming that our findings are replicated by other investigators. As suggested by the experience in aplastic anemia,23 patients who carry either hTERT or hTR mutations are unlikely to have a response to immunosuppression and may be good candidates for immunosuppressive clinical trials. The presence of a diagnostic genetic test gives patients at risk and their clinicians a chance to consider early screening and evaluation tailored to identification of complications of dyskeratosis congenita. Patients with dyskeratosis congenita, especially those with severe forms, have a predisposition to cancers of the skin, hematopoietic system, and oral mucosa.

Finally, telomere length may serve as a surrogate marker for the identification of patients at greatest risk for carrying mutant telomerase genes. In our series of 15 subjects, longer telomeres appeared to predict the absence of a telomerase mutation, although this finding requires verification in larger studies. Since the consequences of carrying mutant telomerase genes can appear in adulthood as either idiopathic pulmonary fibrosis or aplastic anemia without dyskeratosis, the consideration of such cases as part of a syndrome of telomere shortening may heighten the index of suspicion and facilitate diagnosis.

Supported by a grant (NCI K08 118416) from the National Institutes of Health (NIH) (to Dr. Armanios), the Richard C. Ross Johns Hopkins School of Medicine Clinician Scientist Award (to Dr. Armanios), the Maryland Cigarette Restitution Fund (to Johns Hopkins University), a grant from the Johns Hopkins Institute for Cellular Engineering Pilot Program (to Dr. Greider), a grant (HL K08 85406) from the NIH and the Francis Family Foundation (to Dr. Lawson), a grant (AI129524) from the NIH and grants (MOP38075 and GM179042) from the Canadian Institute of Health Research (to Dr. Lansdorp), a Vanderbilt Discovery Grant and the Rudy W. Jacobson endowment (to Dr. Loyd), and a grant (M01 RR-00095) from the National Center for Research Resources of the NIH to support the Vanderbilt Clinical Research Center.

Dr. Lansdorp reports being a founding shareholder in Repeat Diagnostics, a company that specializes in length measurement of leukocyte telomeres with the use of flow FISH. No other potential conflict of interest relevant to this article was reported.

We thank the subjects and their families who participated in this study and their clinicians, especially Drs. Adaani Frost and Keith E. Kelly and nurses Wendi Mason and Rhonda Green; the Johns Hopkins Fragment Analysis Laboratory and Laura Kasch-Semenza for their help with DNA sequencing; Melissa Prince for technical assistance; and Dr. David Valle for his valuable advice.

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Asthma Control during the Year after Bronchial Thermoplasty


From St. Joseph’s Healthcare, McMaster University, Hamilton, ON, Canada (G.C., J.D.M.); Gartnavel General Hospital, University of Glasgow, Glasgow, United Kingdom (N.C.T., R.C.); Irmandade Santa Casa de Misericórdia, Porto Alegre, Brazil (A.S.R.); Wythenshawe Hospital, University of Manchester, Manchester, United Kingdom (R.M.N.); Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, United Kingdom (P.A.C.); Odense University Hospital, Odense, Denmark (H.C.S.); Montreal Chest Institute, Montreal (R.O.); Glenfield General Hospital, University Hospitals of Leicester National Health Service Trust, Leicester, United Kingdom (I.D.P.); London Health Science Centre, London, ON, Canada (D.M.); and Laval Hospital, Laval University, Quebec, QC, Canada (M.L.). Address reprint requests to Dr. Cox at the Firestone Institute for Respiratory Health, St. Joseph’s Healthcare and McMaster University, 50 Charlton Ave. E., Rm. T2123, Hamilton, ON L8N 4A6, Canada, or at copx@mcmaster.ca.

*Members of the Asthma Intervention Research (AIR) Trial Study Group are listed in the Appendix.

ABSTRACT

BACKGROUND
Bronchial thermoplasty is a bronchoscopic procedure to reduce the mass of airway smooth muscle and attenuate bronchoconstriction. We examined the effect of bronchial thermoplasty on the control of moderate or severe persistent asthma.

METHODS
We randomly assigned 112 subjects who had been treated with inhaled corticosteroids and long-acting β₂-adrenergic agonists (LABA) and in whom asthma control was impaired when the LABA were withdrawn to either bronchial thermoplasty or a control group. The primary outcome was the frequency of mild exacerbations, calculated during three scheduled 2-week periods of abstinence from LABA at 3, 6, and 12 months. Airflow, airway responsiveness, asthma symptoms, the number of symptom-free days, use of rescue medication, and scores on the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) were also assessed.

RESULTS
The mean rate of mild exacerbations, as compared with baseline, was reduced in the bronchial-thermoplasty group but was unchanged in the control group (change in frequency per subject per week, −0.16±0.37 vs. 0.04±0.29; P=0.005). At 12 months, there were significantly greater improvements in the bronchial-thermoplasty group than in the control group in the morning peak expiratory flow (39.3±48.7 vs. 8.5±44.2 liters per minute), scores on the AQLQ (1.3±1.0 vs. 0.6±1.1) and ACQ (reduction, 1.2±1.0 vs. 0.5±1.0), the percentage of symptom-free days (40.6±39.7 vs. 17.0±37.9), and symptom scores (reduction, 1.9±2.1 vs. 0.7±2.5) while fewer puffs of rescue medication were required. Values for airway responsiveness and forced expiratory volume in 1 second did not differ significantly between the two groups. Adverse events immediately after treatment were more common in the bronchial-thermoplasty group than in the control group but were similar during the period from 6 weeks to 12 months after treatment.

CONCLUSIONS
Bronchial thermoplasty in subjects with moderate or severe asthma results in an improvement in asthma control. (ClinicalTrials.gov number, NCT00214526.)
Many of the variable symptoms of asthma are thought to be due to the contraction of airway smooth muscle, leading to bronchoconstriction.\textsuperscript{1,2} Increased airway smooth-muscle mass is a characteristic feature of asthma, particularly in persons with severe or fatal asthma.\textsuperscript{3,4} Bronchial thermoplasty is a novel intervention in which controlled thermal energy is delivered to the airway wall during a series of bronchoscopies, resulting in a prolonged reduction of airway smooth-muscle mass.\textsuperscript{5} In previous studies, we determined the amount and duration of energy to be delivered that result in modest thermal injury.\textsuperscript{5,6} The treatment in humans of airways between 3 and 10 mm in diameter led to clinically meaningful reductions in muscle-mediated narrowing of the airway and to improvement of asthma symptoms.\textsuperscript{7,8} We report the results of the yearlong randomized, controlled Asthma Intervention Research (AIR) Trial, which examined the efficacy and safety of bronchial thermoplasty as a treatment for moderate or severe persistent asthma.

**METHODS**

**SUBJECTS**

Persons 18 to 65 years of age were eligible for enrollment if they had moderate or severe persistent asthma, defined according to the guidelines of the Global Initiative for Asthma,\textsuperscript{9} requiring daily therapy with inhaled corticosteroids equivalent to a dose of 200 μg or more of beclomethasone and long-acting β\textsubscript{2}-adrenergic agonists (LABA), at a dose of 100 μg or more of salmeterol (Serevent, GlaxoSmithKline) or the equivalent, to maintain reasonable asthma control. Inclusion criteria were airflow obstruction, assessed as a prebronchodilator forced expiratory volume in 1 second (FEV\textsubscript{1}) of 60 to 85% of the predicted value, and airway hyperresponsiveness, defined by a provocative concentration of methacholine required to lower the FEV\textsubscript{1} by 20% (PC\textsubscript{20}) of less than 8 mg per milliliter, as well as stable asthma during the 6 weeks before enrollment. Stable asthma was defined as an absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance therapy, and stable use of rescue medication (4 puffs or fewer of a short-acting bronchodilator at a dose of 100 μg per puff delivered by a metered-dose inhaler [albuterol or the equivalent]) during 24 hours for symptom relief.

One other criterion in addition to fulfilling the definition of moderate or severe asthma was worsening asthma control after abstention from LABA at baseline for 2 weeks, documented by either an increase of at least 0.5 in the score on the Asthma Control Questionnaire (ACQ)\textsuperscript{10} (on a scale of 0 to 6, with higher numbers indicating worse control), or a decline of 5% in the average morning peak expiratory flow (PEF) during the second week of abstinence, as compared with the mean morning PEF during the week immediately before LABA therapy was withdrawn. Subjects were excluded if they had had three or more lower respiratory tract infections requiring antibiotics during the previous 12 months or a respiratory tract infection within the previous 6 weeks.

**STUDY DESIGN**

This randomized, controlled trial was conducted at 11 centers in four countries. During the 4-week baseline period, subjects continued to receive maintenance therapy with inhaled corticosteroids and LABA for the first 2 weeks, and LABA were then withheld for the next 2 weeks. Therapy with inhaled corticosteroids and LABA was resumed for the treatment period, which lasted for at least 6 weeks and usually no more than 9 weeks, with a subsequent 12-month follow-up period. The study design is shown in Figure 1. All subjects were seen in follow-up at 3 months while receiving treatment with inhaled corticosteroids and LABA. They were asked to refrain from using LABA after this point, unless they had a severe exacerbation (an event requiring treatment with oral corticosteroids, as judged by the investigator, or a decrease in the morning PEF, for 1 or more days, of more than 30% below the average baseline morning PEF recorded during the week immediately preceding withdrawal from LABA therapy), or if they were judged by the investigator to have poor asthma control that required the resumption of LABA. For those subjects whose asthma could be controlled without LABA, evaluations were performed after 6 and 12 months of treatment with inhaled corticosteroids alone. Subjects who needed to resume LABA therapy be-
Figure 1. Study Design.
Seven subjects (three in the bronchial-thermoplasty group and four in the control group) withdrew consent before the 3-month follow-up visit. Six subjects (two in the bronchial-thermoplasty group and four in the control group) withdrew consent for reasons unrelated to the study, and one subject in the bronchial-thermoplasty group refused to abstain from long-acting β₂-agonist (LABA) after the follow-up visit at 6 weeks. Inhaled corticosteroids alone were continued only if the treatment was tolerated. Visits 1 through 3 after baseline and the 6-week follow-up visit are not shown.
fore the visits at 6 and 12 months were evaluated at those assessment points after withdrawal from LABA therapy for 2 weeks.

The study protocol was approved by local or regional ethics review boards at all study sites before the enrollment of any subjects. All subjects provided written informed consent. The study began in November 2002, and the 12-month follow-up period was completed for all subjects by November 2005. An independent data and safety monitoring board oversaw the study.

**RANDOMIZATION**

Eligible subjects were assigned to treatment with inhaled corticosteroids plus LABA (control group) or to treatment with bronchial thermoplasty in addition to inhaled corticosteroids and LABA (bronchial-thermolplasty group) in blocks of four at each center. The randomization code was computer-generated centrally and provided to the study sites in separate envelopes. Investigators were unaware of the block size.

**TREATMENT PERIOD**

Subjects assigned to the bronchial-thermolplasty group underwent three bronchoscopy procedures performed with the use of the Ailair system (Asthmatx) at intervals of approximately 3 weeks. During the procedure, they were under either general anesthesia or conscious sedation, as previously described. A video showing part of an actual procedure is in the Supplementary Appendix, available with the full text of this article at www.nejm.org. Control subjects had three treatment visits at intervals of 3 weeks for clinical review and Spirometric assessment and received a systemic corticosteroid similar to that administered to subjects in the bronchial-thermolplasty group.

**FOLLOW-UP PERIOD**

All subjects in the two groups were seen 2 weeks after each treatment visit. After the last treatment visit (designated as time 0), clinic visits were scheduled at 6 weeks and at 3, 6, and 12 months. Subjects were contacted by telephone on days 1 and 7 after each treatment visit and monthly after the visit at month 3.

**OUTCOME MEASURES**

The primary outcome was the difference between the two groups in the change in the rate of mild exacerbations between baseline and later time points. Exacerbations, ascertained from daily diaries in which subjects recorded events, were defined as at least one of the following occurrences on 2 consecutive days: a reduction in the morning PEF of at least 20% below the average value (based on the PEF recorded during the week immediately preceding the withdrawal of LABA at baseline), the need for more than three additional puffs of rescue medication exceeding the average use during the week immediately preceding the withdrawal of LABA at baseline, or nocturnal awakening caused by asthma symptoms. Only events occurring during the 2-week periods of abstinence from LABA, according to the study protocol, at 3, 6, and 12 months were used to calculate the rates of mild and severe exacerbations.

All subjects kept a daily diary from the beginning of the baseline period to the visit at month 6, and for a 4-week period before the visit at month 12. The data recorded in the diaries were used to assess changes in the PEF, the use of rescue medication, the number of symptom-free days, and the symptom score. The symptom score was the total of the individual scores (on a scale of 0 to 3, with higher numbers indicating more frequent or more severe symptoms or both) for nighttime wheezing and cough and daytime wheezing, cough, breathlessness, and sputum production. These six individual scores were summed to yield a maximum possible score of 18. A symptom-free day was defined as a day during which the symptom score was 0 and there was no nighttime awakening. The ACQ consists of six questions and the measurement of prebronchodilator FEV1, and responses are scored on a scale of 0 to 6, with lower numbers indicating better asthma control. The minimal important change in the score is thought to be 0.5. The Asthma Quality of Life Questionnaire (AQLQ) consists of 32 items covering asthma-related symptoms and limitations during the 2 weeks preceding administration of the questionnaire, and responses are scored on a scale of 1 to 7, with higher numbers indicating a better quality of life. The minimal important change in the score is thought to be 0.5. For details of the outcome measures, see the Supplementary Appendix.

**MONITORING ADVERSE EVENTS**

At each visit and during each telephone call, subjects were asked by research staff about potential adverse events, and their daily diaries were exam-
ined by study personnel to ensure complete reporting of events. Adverse events were classified as respiratory or nonrespiratory events and were reported at baseline and for the treatment period and the post-treatment period.

**Statistical Analysis**

The statistical analysis was performed on an intention-to-treat basis and included those subjects who completed at least one bronchoscopy session or treatment visit. The study was powered to detect differences between the two groups in the change from baseline to later time points. There was no imputation of missing data. Frequencies of adverse events were compared with the use of Fisher’s exact test. For continuous variables, statistical significance was determined with the use of Student’s t-test, and for categorical variables, statistical significance was determined with the use of the Cochran–Mantel–Haenszel test. P values of less than 0.05 were considered to indicate statistical significance. Data are reported as means (±SD), and all reported P values are two-sided, unless otherwise indicated.

The study was designed with more than 90% power to detect a difference of eight mild exacerbations per subject per year between the two groups with the use of a two-tailed t-test. Exacerbation rates and secondary outcomes were analyzed on the basis of the change from the baseline period (the 2-week period during which the subjects were treated with inhaled corticosteroids alone) to the 2-week periods at 3, 6, and 12 months during which they were treated with inhaled corticosteroids alone (Fig. 1). For the analysis of the effects of bronchial thermoplasty in addition to usual care, at 3 months, the relevant baseline was treatment with inhaled corticosteroids plus LABA. Data for all subjects were included in the safety analyses.

The protocol was designed by a committee of academic authors and employees of the sponsor, with comment in specific areas from an advisory board. The database was managed and all analyses requested by the investigators were performed by QST Consultations. The manuscript was written by the corresponding author, with contributions from all coauthors and selected employees of the sponsor, and was reviewed by the external advisory board. The final manuscript was prepared by the corresponding author, without limitation by the sponsor. All the authors vouch for the accuracy and completeness of the reported data.

**Results**

**Baseline Characteristics of the Subjects**

Of 240 subjects who underwent screening, 68 did not fulfill all the entry criteria on assessment during the run-in period and 60 did not complete the phase of withdrawal from LABA (i.e., could not tolerate withdrawal, did not have deterioration, or withdrew consent). The remaining 112 subjects underwent randomization, and 56 subjects were assigned to each of the two study groups (Fig. 1). Outcomes for the effect of bronchial thermoplasty in addition to usual care were assessed at 3 months for 52 subjects in the bronchial-thermoplasty group and 48 control subjects; complete data after 12 months of follow-up were available for 52 subjects in the bronchial-thermoplasty group and 49 in the control group (Fig. 1). The baseline demographic characteristics of the two groups were similar (Table 1). For the statistical comparisons, baseline means were calculated only for subjects for whom follow-up data were available.

**Exacerbations**

Twelve months after the last study treatment, the mean number of mild exacerbations in the bronchial-thermoplasty group was 0.18±0.31 per subject per week, as compared with 0.35±0.32 at baseline. The number of mild exacerbations in the control group was 0.31±0.46 per subject per week, as compared with 0.28±0.31 at baseline. The difference between the two groups in the change from baseline was significant at 3 months and at 12 months (P=0.03 for both comparisons) but not at 6 months (Fig. 2). As compared with baseline, the average number of exacerbations during the 2-week periods at 3, 6, and 12 months when subjects in the two groups were treated with inhaled corticosteroids alone was reduced in the bronchial-thermoplasty group but was not significantly changed in the control group (−0.16±0.37 vs. 0.04±0.29 per subject per week, P=0.005 for the comparison between the groups). Analysis with the use of the Wilcoxon rank-sum method also showed a significant difference between the groups (P=0.01). This finding can be extrapolated to approximately 10 fewer mild exacerbations per subject per year in the bronchial-thermoplasty group.
Twelve months after the last study treatment, the mean number of severe exacerbations in the bronchial-thermoplasty group was 0.01±0.08 per subject per week, as compared with 0.07±0.18 at baseline. The number of severe exacerbations in the control group was 0.06±0.24 per subject per week, as compared with 0.09±0.31 at baseline. The difference between the two groups in the change from baseline was not significant at any time point (Fig. 2).

Changes in the secondary outcomes (airflow, airway hyperresponsiveness, use of rescue medication, asthma symptoms, and scores on the AQLQ and ACQ) in the subjects receiving usual
Bronchial Thermoplasty in Asthma

HIGH-DOSE INHALED CORTICOSTEROIDS
In a post hoc analysis, data for a subgroup of subjects requiring high maintenance doses of inhaled corticosteroids (>1000 μg of beclomethasone or the equivalent) at baseline were analyzed separately and showed greater differences between the control group and the bronchial-thermoplasty group. Data on this analysis are in the Supplementary Appendix.

ADVERSE EVENTS
There was an increase in adverse respiratory events in subjects undergoing bronchial thermoplasty immediately after the procedure, with a return to baseline values during the post-treatment period. During the treatment period, there were 407 adverse respiratory events, of which 69% were mild, 28% were moderate, and 3% were severe. In the control group there were 106 adverse respiratory events, of which 69% were mild, 30% were moderate, and 1% were severe. The most frequently observed adverse events during the treatment period are listed in Table 2. In the bronchial-thermoplasty group, the majority of the adverse events occurred within 1 day after the procedure and resolved an average of 7 days after the onset of the event.

Hospitalizations for adverse respiratory events during the treatment period were more frequent in the bronchial-thermoplasty group (four subjects required a total of six hospitalizations) than in the control group (two subjects required one hospitalization each). Four of the hospitalizations during the bronchial-thermoplasty group were for exacerbation of asthma (one within 1 day after treatment, two 30 days after treatment, and one 85 days after treatment), one was for partial collapse of the left lower lobe (2 days after treatment), and one was for pleurisy (43 days after treatment).

During the post-treatment period, the proportion of subjects with adverse respiratory events was similar in the two groups (Table 2). The rate of hospitalization for respiratory events was low during this period and did not differ significantly between the two groups: three subjects in the bronchial-thermoplasty group required hospitalization — one for chest infection and two for asthma exacerbation — and two subjects in the control group required a total of three hospitalizations for increased asthma symptoms. There were no deaths during the study.

Although there were variations among the study centers in the size of the treatment effect and the number of adverse events, there was no obvious relationship between the investigators’ experience with bronchial thermoplasty or the numbers of subjects treated and the outcomes or adverse events. One additional hospitalization for an adverse respiratory event occurred 14 months...
after bronchial thermoplasty in a subject who had undergone the procedure uneventfully and had completed the trial with normal spirometric values and good asthma control (score on the ACQ, 0.2; symptom score, 0), but who subsequently underwent resection for an abscess in a left upper lobe. Histologic examination did not reveal obstruction or any other potentially contributory abnormality in the airways as a result of thermoplasty. (For information on the follow-up in the bronchial-thermoplasty group after completion of the study, see the Supplementary Appendix.)

**DISCUSSION**

This randomized, controlled study examined the efficacy and safety of bronchial thermoplasty in subjects with moderate or severe persistent asthma. The study design was based on the hypothesis that if bronchial thermoplasty were beneficial,
then in subjects treated with bronchial thermoplasty, as compared with control subjects, asthma control would be improved when treatment with LABA was discontinued. Although the benefits of bronchial thermoplasty were obvious when LABA were withdrawn, they were also observed at 3 months, when all subjects in the two study groups were still receiving LABA (Fig. 3). Among subjects treated with inhaled corticosteroids alone, bronchial thermoplasty reduced the frequency of mild exacerbations at a rate equivalent to 10 exacerbations per subject per year and provided 86 additional symptom-free days per subject per year. These improvements were achieved during a period in which the use of rescue medication was reduced in the bronchial-thermoplasty group, as compared with the control group.

The effect of bronchial thermoplasty was evident 3 months after the procedure. The improvements in objective and subject-centered outcomes did not diminish over the course of the study, and the outcomes assessed at 1 year showed the same degree of improvement as at 3 months. In a preliminary, nonrandomized study, we found that the benefits of bronchial thermoplasty persisted at 2 years. Thus, although the duration of the effect of bronchial thermoplasty remains uncertain, in this study the benefit appeared to persist at 1 year.

Treatment with bronchial thermoplasty was associated with adverse events related primarily to worsening of asthma symptoms during the period immediately after treatment. Although the frequency of adverse events was similar in the two groups at 6 weeks to 1 year after bronchial thermoplasty, studies of larger numbers of patients and with a longer follow-up will be needed to rule out less common adverse events than those identified in this study.
The interpretation of our results is confounded by the nonblinded study design; this limitation is important, given that bronchial thermoplasty is a procedure that may increase the potential for a strong placebo effect. However, the magnitude and persistence of the effects of the intervention observed are probably greater than what could be attributed to placebo alone. For example, a within-group change of 0.5 in scores on the AQLQ is considered clinically significant, and we found a between-group difference of 0.69 at 12 months. Of the outcomes reported, perhaps the two that are least susceptible to bias are the morning PEF, since it was measured daily for

<table>
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<th>Bronchial-Thermoplasty Group</th>
<th>Control Group</th>
<th>P Value†</th>
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<td>Frequency of Event</td>
<td>Subjects with Event</td>
<td>Frequency of Event</td>
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<td>Night awakenings</td>
<td>3.3</td>
<td>12.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>3.3</td>
<td>10.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.9</td>
<td>10.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>2.5</td>
<td>9.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>2.5</td>
<td>9.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1.3</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>1.3</td>
<td>3.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Subjects were asked about adverse events at each office visit and during telephone calls. Only adverse events occurring in the bronchial-thermoplasty group at a frequency of 1.0% or greater are listed.
† For the comparison between the two groups of the number of subjects reporting an adverse event, P values were calculated with the use of Fisher’s exact test.
most of the study period, and the number of mild exacerbations per subject per week, since these were counted after the study had ended by a statistician who reviewed the data in the daily diaries, according to predetermined criteria. The increase in the morning PEF value of 39 liters per minute from baseline to 12 months among subjects treated with bronchial thermoplasty (between-group difference, 31 liters per minute) exceeded the change seen in placebo groups in other trials involving patients with asthma (range, –22 to 17 liters per minute).17–21 Our data showing potential beneficial effects of bronchial thermoplasty provide the basis for mounting a placebo-controlled trial involving the use of sham bronchial thermoplasty.

Supported by Asthmatx.

All authors received financial support from Asthmatx for the completion of this study. Dr. Cox reports receiving lecture fees from Novartis, Merck Frosst, Asthmatx, GlaxoSmithKline, and AstraZeneca, fees for serving on advisory boards from GlaxoSmithKline and AstraZeneca, and grant support from AstraZeneca and GlaxoSmithKline; Dr. Thomson, grant support from AstraZeneca and GlaxoSmithKline; Dr. Moseley, grant support from GlaxoSmithKline; Dr. Altana, lecture fees from GlaxoSmithKline; Dr. Pavord, lecture fees from GlaxoSmithKline and AstraZeneca and grant support from GlaxoSmithKline; and Dr. Niven, lecture fees from Altana, Novartis, GlaxoSmithKline, and AstraZeneca and grant support from Wyeth. No other potential conflict of interest relevant to this article was reported.

We thank Alan Left (University of Chicago, Chicago), Nizar Jarjour (University of Wisconsin, Madison), Elliot Israel (Brigham and Women’s Hospital, Boston), Monica Kraft (Duke University, Durham, NC), Louis-Philippe Bouler (Laval University, Quebec, QC), and Mario Castro (Washington University, St. Louis) for their valuable contributions to the design and interpretation of this study; and Michael Lafer, who pioneered the concept of bronchial thermoplasty for the treatment of asthma.

APPENDIX

Members of the AIR Trial Study Group were as follows: data and safety monitoring board — W. Busse, R. Schellenberg, A.S. Slutsky (chair); coinvestigators and study coordinators — Canada: McMaster University: P. Nair, S. Goodwin, K. Currie; Montreal Chest Institute: J. Bourbeau, F. Houghton; London Health Science Centre: N. Patterson, S. Metha, J. Howard, L. MacBean; Laval University: S. Martel, L-P. Boulet, L. Morel, L. Trepianier; United Kingdom: University of Glasgow: S. Bicknell, E. Livingstone, J. Lafferty; University of Manchester: C. Prys-Picard, G. Fletcher; Newcastle University: B. Higgins, T. Small, B. Foggio; University of Leicester: M. Berry, D. Shaw, N. Sheldon; London Chest Hospital: N. Barnes (investigator), D. Watson; Brazil: Santa Casa: P.G. Cardoso, P.R.D. Soares; Denmark: Odense University Hospital: F. Rasmussen, H.M. Christensen, M. Olsen.

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Varicella–Zoster Vaccine for the Prevention of Herpes Zoster

David W. Kimberlin, M.D., and Richard J. Whitley, M.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors’ clinical recommendations.

A 64-year-old man presents to his internist for his annual examination. He has been in good general health, although he received a diagnosis of pneumonia 8 months ago, for which he was treated with a course of oral antibiotics. At this visit, he inquires about when he should receive the “pneumonia shot” and whether other vaccinations are recommended. Should he receive the varicella–zoster vaccine?

Varicella–zoster virus (VZV) is a herpesvirus that causes two distinct clinical syndromes. Primary infection is manifested as varicella (chickenpox), whereas reactivation of latent VZV results in a localized eruption known as herpes zoster (shingles) (Fig. 1). VZV is a highly contagious pathogen. Before licensure of the varicella vaccine for children in the United States, 95.5% of people 20 to 29 years of age, 98.9% of people 30 to 39 years of age, and more than 99.6% of people 40 years of age or older had evidence of previous VZV infection.

Herpes zoster develops in approximately 30% of people over a lifetime. The annualized incidence of herpes zoster ranges from approximately 1.5 to 4.0 cases per 1000 persons with up to 1 million cases or more each year in the United States. The risk of disease increases with age, beginning at about 50 years; herpes zoster is 8 to 10 times as likely to develop in people 60 years of age or older as in younger people. One or more episodes of herpes zoster will have developed in up to half of people who are 85 years of age. Herpes zoster also occurs with increased frequency in immunocompromised patients, especially those with human immunodeficiency virus (HIV) infection.

Complications of herpes zoster in immunocompetent hosts include postherpetic neuralgia, encephalitis, myelitis, cranial-nerve palsies, and peripheral-nerve palsies. Postherpetic neuralgia, a persistent pain syndrome occurring after the resolution of the zoster rash, is perhaps the most challenging and debilitating complication; it can last for weeks, months, or even years. Although the development of postherpetic neuralgia can occur at any age, people 50 years of age or older are most likely to have this complication, and more than 40% of people older than 60 years of age who have had zoster have postherpetic neuralgia. Approximately 100,000 to 200,000 new cases of postherpetic neuralgia occur in the United States every year.

After the primary VZV infection (chickenpox), latent infection is established in the sensory-nerve ganglia (Fig. 2). The trigeminal and thoracic ganglia are the most
common neuronal sites involved; these dermatomes are also the most common sites of cutaneous herpes zoster.\(^3\) Latent VZV DNA is extrachromosomal, but the overall viral burden in ganglionic cells is low.

As shown in Figure 3, the decline in cell-mediated immunity over time as people age confers a predisposition to the occurrence of herpes zoster in older adults.\(^4,7,20-26\) Second episodes of herpes zoster in immunocompetent people are uncommon, probably because of the decreased responsiveness of older people to vaccination in general. As a result, a new VZV vaccine (Zostavax, Merck) was developed specifically for protection against herpes zoster. The commercially available zoster vaccine contains a minimum of 19,400 plaque-forming units per dose.\(^31\) In contrast, the minimum levels of VZV in the commercially available chickenpox vaccines are either 9772 plaque-forming units per dose (in the quadrivalent measles, mumps, rubella, and varicella vaccine [ProQuad, Merck])\(^32\) or 1350 plaque-forming units per dose (in the monovalent varicella vaccine [Varivax, Merck]).\(^33\)

The preventive effect of the zoster vaccine is thought to be a consequence of its boosting effect on an older person’s cell-mediated immunity to VZV,\(^34\) mimicking the immunologic benefits of the exposure of a VZV-immune adult to chickenpox. This pharmacologic boost increases cell-mediated immunity to a new set point above the “immunologic threshold” below which a person is at risk for zoster (Fig. 3).

The histologic changes in the skin lesions are similar to those of varicella. Multinucleated giant cells and intranuclear inclusions are present in the skin, and a mononuclear inflammatory infiltrate occurs in the dorsal-root ganglion of the affected dermatome. Necrosis of ganglion cells and demyelination of the corresponding axon occur.\(^28,29\)

The VZV vaccine, originally developed and licensed as the “chickenpox vaccine” to prevent varicella, is a live attenuated vaccine that is effective in preventing primary infection with wild-type VZV. However, initial studies suggested that to elicit a significant and durable increase in cell-mediated immunity in older adults, a higher titer of live attenuated virus would be required,\(^30\) probably because of the decreased responsiveness of older people to vaccination in general. As a result, a new VZV vaccine (Zostavax, Merck) was developed specifically for protection against herpes zoster. The commercially available zoster vaccine contains a minimum of 19,400 plaque-forming units per dose.\(^31\) In contrast, the minimum levels of VZV in the commercially available chickenpox vaccines are either 9772 plaque-forming units per dose (in the quadrivalent measles, mumps, rubella, and varicella vaccine [ProQuad, Merck])\(^32\) or 1350 plaque-forming units per dose (in the monovalent varicella vaccine [Varivax, Merck]).\(^33\)

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**Clinical Evidence**

Several small clinical studies have shown that immunization with a varicella vaccine boosts waning cell-mediated immunity in older adults.\(^35-37\) A large efficacy study by the Shingles Prevention Study Group evaluated the high-titer, live attenuated zoster vaccine.\(^10\) A total of 38,546 subjects 60 years of age or older were enrolled and followed for a mean period of 3 years. The subjects were stratified according to age at enrollment (60 to 69 years or ≥70 years). More than 95% of the subjects were followed until completion of the study. The
incidence of herpes zoster was 51% lower in the group of subjects who received the vaccine than in the group of subjects who received placebo (5.4 cases per 1000 person-years vs. 11.1 cases per 1000 person-years, P<0.001). Vaccine-strain DNA was not detected in any of the subjects with zoster. The incidence of postherpetic neuralgia was 67% lower among subjects who received the vaccine than among those who received placebo (0.5 case per 1000 person-years vs. 1.4 cases per 1000 person-years, P<0.001). The median duration of pain among subjects in whom herpes zoster developed was shorter in the vaccine group than in the placebo group (21 days vs. 24 days, P = 0.03), and the degree of pain also was lower among the vaccine recipients (P = 0.008).

The vaccine was more efficacious in preventing herpes zoster among persons who were 60 to 69 years of age than among those who were 70 years or older. However, it prevented postherpetic neuralgia to a greater extent among those who were 70 years or older than among those who were 60 to 69 years old.

**Clinical Use**

On May 25, 2006, the Food and Drug Administration licensed the zoster vaccine for the prevention of herpes zoster in persons 60 years of age or older. It is not indicated for the treatment of herpes zoster or postherpetic neuralgia.

The zoster vaccine should not be administered to persons with a history of anaphylactic or anaphylactoid reactions to gelatin, neomycin, or any other vaccine component. People with a history of primary or acquired immunodeficiency conditions or those receiving immunosuppressive therapy, including corticosteroids, should not receive the vaccine. Zoster vaccination is also contraindicated in people with active, untreated tuberculosis and in pregnant women.

There are no alternatives to the zoster vaccine for prophylaxis. The other available varicella-containing vaccines, Varivax and ProQuad, contain significantly lower titers of live attenuated virus and therefore are of insufficient potency to elicit an increase in cell-mediated immunity to VZV in older adults. These vaccines should not be administered to older adults to prevent herpes zoster or postherpetic neuralgia.

Antiviral therapy decreases “zoster-associated pain” (the continuum of pain measured from its onset to final resolution, including postherpetic neuralgia), but it does not prevent the development of postherpetic neuralgia. Opioids, tricyclic antidepressants, and gabapentin have been
shown to have limited effectiveness in reducing the severity or duration of postherpetic neuralgia, with variable and frequently inadequate results clinically.

The zoster vaccine, which is frozen for storage, is administered subcutaneously as a single 0.65-ml dose. To minimize the loss of potency, it should be administered immediately after reconstitution with the supplied diluent; if not used within 30 minutes after reconstitution, the vaccine should be discarded. There are insufficient data to suggest that repeated administration of the zoster vaccine is safe or confers an additional benefit.

On the basis of a cost of $150 for the single-shot vaccine, a preliminary Centers for Disease Control and Prevention (CDC) analysis has shown that the estimated “societal perspective” cost per quality-adjusted life-year ranges from $14,877 to $34,852. Approximately 17 people would need to be vaccinated in order to prevent one case of herpes zoster, and approximately 31 would need to be vaccinated in order to prevent one case of postherpetic neuralgia. The cost per case of herpes zoster prevented is estimated to be $3,330, and the cost per case of postherpetic neuralgia prevented is estimated to be $6,405.

ADVERSE EFFECTS

Most of the information regarding the adverse effects of the zoster vaccine comes from the Shingles Prevention Study. Within the first 42 days after vaccination, varicella-like rashes at the injection site were more likely to develop in vaccine recipients than in placebo recipients (0.1% vs. 0.04%, P<0.05). Other symptoms and signs at the site of injection that occurred more frequently in the first 42 days in vaccine recipients than in placebo recipients included erythema (36% vs. 7%), localized pain or tenderness (35% vs. 9%), swelling (26% vs. 5%), and pruritus (7% vs. 1%) (P<0.05 for all four comparisons). The number and types of serious adverse events in the first 42 days were similar between the two groups. According to the package insert, cardiac events occurred more often among the vaccine recipients than among the placebo recipients in the Shingles Prevention Study (0.6% vs. 0.4%); whether this increased occurrence was due to the zoster vaccine and, if so, the reason or reasons for it are not known.

Since the zoster vaccine has been clinically available for less than 1 year, the potential risk of rare adverse events is unknown. The longer experience with the pediatric varicella vaccine (more than 10 years) suggests that this risk may be small, although the potency of the zoster vaccine is higher and the target population is quite different.

AREAS OF UNCERTAINTY

There are several areas of uncertainty. First, ongoing analyses of cost-effectiveness probably will influence recommendations for zoster immunization for people 60 years of age or older.

Second, it is unclear whether people 50 to 59 years of age should receive the vaccine. This would be an off-label use of the product. An argument for such use is the fact that the burden of herpes zoster in this population is substantial, since the incidence of zoster increases among people 50 years of age or older. Furthermore, the efficacy of the vaccine against herpes zoster is higher among persons 60 to 69 years of age than among those 70 years or older, suggesting that it may be more immunogenic in people 50 to 59 years of age as well. However, no efficacy data are available for this population, and the available immunogenicity data are based only on small numbers of people in this age group.

Third, wild-type VZV infections are declining...
as a result of universal vaccination in childhood, including a second dose of vaccine at 4 to 6 years of age, as recommended recently by the CDC Advisory Committee on Immunization Practices (ACIP) and by the Committee on Infectious Diseases of the American Academy of Pediatrics.\(^4\,\text{a},\,\text{b}\)

As a consequence, the likelihood that older people will be “boosted” by exposure to a child with chickenpox is declining. The effect that this shift in the epidemiology of VZV will have at a time when older people are also receiving the zoster vaccine will require careful postlicensure monitoring over a period of many years. Questions to be answered include the incidence of herpes zoster over time and the longevity of protection conferred by the one dose of the zoster vaccine currently indicated. As these questions are being investigated, persons who have previously received Varivax or ProQuad should be considered to be candidates for zoster vaccination as they grow older, unless there is an applicable precaution or contraindication.

Fourth, the zoster vaccine is not licensed for use in immunocompromised people. However, this population is at especially high risk for the development of herpes zoster. This group includes people who are mildly immunosuppressed, such as people with diabetes and people receiving low-dose corticosteroids, tumor-necrosis-factor blockers, and other immunomodulatory drugs. In addition, the safety and efficacy of the vaccine have not been established in immunocompetent people for whom immunosuppressive therapy is anticipated and who will therefore be at high risk for herpes zoster. This group includes patients who are awaiting organ transplantation, patients with early-stage HIV infection who are asymptomatic, and patients who will be receiving chemotherapy for cancer or immunosuppressive therapy for rheumatoid arthritis, lupus, or other autoimmune diseases.

Finally, the efficacy of the vaccine in people who have had a previous episode of herpes zoster is unknown, since this population was excluded from the large zoster vaccine trial.

## Guidelines

In October 2006, the ACIP voted to recommend a single dose of zoster vaccine for adults 60 years of age or older, whether or not they have had a previous episode of herpes zoster.\(^6\) Furthermore, persons with chronic medical conditions may be vaccinated unless there is an applicable precaution or contraindication. Because virtually all adults 60 years of age or older will have had clinical or subclinical primary VZV infection (chickenpox),\(^3\) it is not necessary to determine whether there is a history of chickenpox for routine vaccination of people in this age group.

## Recommendations

The patient described in the vignette is a healthy, immunocompetent person who is 60 years of age or older and is therefore an appropriate candidate for immunization with the zoster vaccine. We recommend that the vaccine be universally administered to such persons, provided there is no contraindication. We do not recommend routine vaccination of people 50 to 59 years of age because of the lack of efficacy data and cost-effectiveness information for this population.

Supported by contracts with the National Institute of Allergy and Infectious Diseases (N01-Al-30025, N01-Al-65306, N01-Al-15113, and N01-Al-62554), and by grants from the General Clinical Research Center Program (M01-RR00032) and the State of Alabama.

Dr. Whitley reports chairing the data and safety monitoring board for the Shingles Prevention Study, serving on the Gilead Sciences Scientific Advisory Board, and receiving speaking fees from Novartis and GlaxoSmithKline. Dr. Kimberlin reports serving as the liaison from the Committee on Infectious Diseases of the American Academy of Pediatrics to the CDC ACIP. No other potential conflict of interest relevant to this article was reported.

We dedicate this review to Stephen Straus, M.D. Dr. Straus’s career achievements in herpes virology in general and in VZV in particular have been seminal to advancing our understanding of disease pathogenesis, treatment, and prevention.

## References

7. Ragozzino MW, Melton LJ III, Kurland LT, Chu CP, Perry HO. Population-

Copyright © 2007 Massachusetts Medical Society.
INHALED SHORT-ACTING $\beta_2$-AGONISTS ARE INDICATED FOR SHORT-TERM relief of symptoms related to bronchospasm in patients with asthma and chronic obstructive pulmonary disease (COPD). Albuterol (called salbutamol outside the United States) is delivered by a metered-dose inhaler, the most widely used drug and delivery method in this class of agents worldwide. In the United States, about 52 million prescriptions for albuterol are filled annually, mostly as generic products containing chlorofluorocarbon (CFC) propellants, making it the seventh most commonly prescribed medication in the country. A similar number of albuterol metered-dose inhalers are prescribed in Europe, most containing a hydrofluoroalkane (HFA) propellant. Dry-powder albuterol inhalers are available in 66 countries but not in the United States.

The transition from CFC to HFA propellants is occurring because of public health concerns about the detrimental effects of CFCs on stratospheric ozone levels. In 2005, the Food and Drug Administration (FDA) ruled that the sale of CFC albuterol metered-dose inhalers would be prohibited in the United States after 2008. Market forces, particularly the limited availability of CFCs, may lead to an earlier transition to HFA albuterol inhalers. Health care providers should understand the reasons for this change and be informed about how these inhalers compare with CFC albuterol inhalers.

POLITICAL AND REGULATORY MANDATES

CFCs are not naturally occurring substances. When developed in the 1890s (Table 1), CFCs were recognized as nonflammable, nontoxic replacements for the hazardous fluids then being used. Their use in home refrigerators began in 1928. By the middle of the 20th century, CFCs were widely used as foam-blowing agents, industrial solvents, cleaning agents, and aerosol propellants. In 1971, Lovelock found CFC-11 in the atmosphere and suggested that CFCs were not being decomposed and were accumulating. Three years later, Molina and Rowland provided a clear explanation for the accumulation of CFCs in the stratosphere and for the effect of this accumulation on stratospheric ozone levels (Fig. 1); their findings were acknowledged in 1995 with the Nobel Prize in Chemistry, an award they shared with Paul Cruzen. Unlike tropospheric ozone, which contributes to the harmful effects of air pollution, stratospheric ozone plays an important role in protecting human health by absorbing ultraviolet B radiation before it can reach the earth’s surface. Although small amounts of ultraviolet B radiation are needed to catalyze vitamin D production, excessive exposure leads to sunburn, skin cancer, photokeratitis, cataracts, and possibly immune suppression. The World Health Organization estimated that a 10% decrease in stratospheric ozone levels would lead to an additional 300,000 nonmelanoma and 4500 melanoma skin cancers worldwide annually; a 1% decrease would
increase the incidence of cataracts by 0.5%. Excessive ultraviolet B radiation at the earth’s surface also has other detrimental environmental effects, including harm to phytoplankton and plants.

The accumulation of CFCs in the stratosphere aroused public health concerns. By 1978, the Environmental Protection Agency (EPA), in conjunction with the FDA, had prohibited the use of CFCs as propellants in self-pressurized containers (e.g., aerosol products such as hair spray), except for use in inhalers. In 1987, the United States and 26 other countries signed the Montreal Protocol, which called for a 50% reduction in the use of ozone-depleting substances (ODSs), including CFCs, by 1998. However, concerns about worsening stratospheric ozone depletion led to amendments to the protocol calling for developed nations to cease use of ODSs entirely by 1996. A total of 188 countries, including the United States, have signed the Montreal Protocol, and international action has been highly successful in reducing ODS use worldwide.

The protocol temporarily exempted from this ban “essential-use” ODSs, defined as those substances that are necessary for health and safety or critical to the functioning of society and for which no technically or economically feasible alternatives exist. Each signatory nation annually submits a proposal indicating the amounts of ODSs required for its own essential use, for review and approval by the protocol’s Technology and Economic Assessment Panel. In the United States, the EPA, advised by the FDA, is responsible for this proposal. The two ODSs currently allowed for essential use in the United States are methyl chloroform, for use in the space shuttle and Titan rocket, and CFCs for metered-dose inhalers.

In 1989, pharmaceutical companies interested in metered-dose inhalers formed a coalition to develop alternative propellants. This combined effort, carried out in cooperation with worldwide regulatory agencies, identified tetrafluoroethane (HFA-134a) as a propellant that could be used in the reformulation of albuterol. Although HFA-134a, like CFCs, is a greenhouse gas, it does not cause ozone depletion. In 2005, the FDA stipulated that essential-use status for CFC albuterol inhalers would be withdrawn at the end of 2008, contingent on the availability of two HFA albuterol inhalers with substantial marketing histories (Proventil HFA, Schering-Plough, and Ventolin HFA, GlaxoSmithKline). More recently, a third HFA albuterol inhaler has been marketed (ProAir HFA, IVAX), as has an HFA inhaler containing levalbuterol (Table 2). The transition from CFC to HFA albuterol inhalers in the United States comes after Australia, Canada, Japan, and the European Union have designated CFCs as nonessential-use ODSs in the manufacture of albuterol inhalers (see Table A in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Coincident with this regulatory decision has been a substantial decrease in essential-use allowances for CFCs in the United States. Some manufacturers have stopped CFC albuterol production because CFCs have become difficult to obtain. Therefore, even before the regulation deadline, full transition from CFC to HFA albuterol products in the United States is possible before the end of 2008.

### Table 1. Timeline of Events Leading to Withdrawal of CFC Inhalers.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1890s</td>
<td>Fluorocarbon chemistry is developed, and CFCs are invented.</td>
</tr>
<tr>
<td>1928</td>
<td>CFC-12 is selected as a refrigerant by Frigidaire for home refrigerators.</td>
</tr>
<tr>
<td>1956</td>
<td>Metered-dose inhalers using CFCs as propellants are introduced into clinical practice.</td>
</tr>
<tr>
<td>1971</td>
<td>CFC-11 is detected in the atmosphere.</td>
</tr>
<tr>
<td>1974</td>
<td>Molina and Rowland postulate that the decline in stratospheric ozone is related to CFCs.</td>
</tr>
<tr>
<td>1978</td>
<td>The FDA finalizes Regulation 21 CFR 2.125, which bans the use of CFCs in all FDA-regulated products, except when medically essential.</td>
</tr>
<tr>
<td>1987</td>
<td>The United States signs the Montreal Protocol on substances that deplete the ozone layer.</td>
</tr>
<tr>
<td>1989</td>
<td>The International Pharmaceutical Aerosol Consortium is established, and HFA-134a is suggested as a replacement for CFCs in inhalers.</td>
</tr>
<tr>
<td>1996</td>
<td>The first metered-dose inhaler containing a non-CFC propellant (Proventil HFA) is approved for use in the United States.</td>
</tr>
<tr>
<td>2008</td>
<td>The FDA-mandated date after which CFC albuterol inhalers can no longer be sold.</td>
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</tbody>
</table>
This transition raises important questions. How does HFA albuterol reformulation affect the pharmaceutical performance of the inhaler? Is the efficacy and safety profile of CFC albuterol maintained with HFA albuterol inhalers? What will be the cost to patients as manufacturers shift from selling the generally inexpensive, generic CFC albuterol to selling brand-name HFA albuterol products?

**Differences in CFC and HFA Inhalers**

HFA inhalers were designed to be used in the same way CFCs inhalers are used (see video, available with the full text of this article at www.nejm.org). The HFA inhalers provide the same amount of albuterol base, 90 μg per puff, as the CFC inhalers, with generally similar particle-size distribution. However, patients may find that the HFA inhaler has a different taste (a result of differences in the propellant and elastomers and excipients) and feel (because the spray emitted from the actuator has less force and a smaller plume). In addition, because of differences in spray characteristics, HFA inhalers may result in greater deposition in the lungs than CFC inhalers. Differences in serum levels of albuterol are not detectable after a standard 2-puff dose, but after 12 puffs, the HFA inhaler produces higher plasma levels of albuterol than the CFC inhaler.

The different spray characteristics of the HFA inhaler may affect delivery of albuterol to the lungs when the inhaler is used with an aerosol inhalation spacer device. With its less forceful spray and smaller plume, the HFA inhaler may deposit a smaller amount of albuterol in the spacer; consequently, more albuterol may be inhaled. However, the interaction of inhalers with spacers is complicated by performance differences in spacers and formulations within the inhaler, as well as by the development of electrostatic charges, which increase the deposition of albuterol within the spacer. Cleaning a spacer with a household detergent reduces the electrostatic charge and improves delivery of both CFC and HFA albuterol. The effect of spray differences between HFA and CFC albuterol inhalers on their performance with spacers has not been adequately explored. Clinical data are not available on the delivery of HFA albuterol through ventilator circuits. However, in an in vitro neonatal lung model, there were no differences in lung delivery between CFC and HFA inhalers when the drug was administered by a spacer through a ventilator circuit.

Clogging of HFA albuterol actuators has been reported, but this is a potential problem with all metered-dose inhalers, including CFC albuterol inhalers. HFA inhalers perform reliably if cleaned at least once a week by removing the metal canister, running warm water through the plastic actuator for 30 seconds, shaking the actuator to remove excess water, and then allowing it to air-dry. However, if a reduction in the force of emitted spray is noted, the actuator should be recleaned. Patients should be advised not to immerse an HFA albuterol canister in water to determine whether the canister is empty; this is not a reliable method for determining the number of metered doses remaining and water may enter the stem and obstruct the spray. With the exception of Ventolin...
HFA, which has a counter, it is difficult to determine when the inhaler is nearly empty. Patients should be advised to keep a spare on hand.

The excipients added to the propellant formulation differ according to the brand of HFA inhaler. For instance, each puff of Proventil HFA releases 4 μl of ethanol. This small amount of ethanol will not have a discernible clinical effect, but it may be of concern for patients who for religious or other reasons abstain from alcohol. Breath-alcohol levels of up to 35 μg per 100 ml may be detected for up to 5 minutes after two puffs of Proventil HFA.23 Unlike CFC propellants, HFA propellants may cause false positive readings in anesthetic gas-monitoring systems.24 The infrared spectrums of HFA overlap with commonly used anesthetic gases in the range of 8 to 12 μm.

One albuterol product, Ventolin HFA, contains no excipients other than the propellant, a characteristic that may improve tolerability for some patients. However, Ventolin HFA comes packaged in a moisture-resistant protective pouch containing a desiccant and has a limited shelf life once it has been removed from the pouch (Table 2). Ventolin HFAs have a greater affinity for moisture than do CFCs,25 which means that water vapor is more likely to enter the canister around the metering-valve gaskets. The other approved HFA inhalers are less susceptible to moisture permeation and do not require a protective pouch.

The reformulation of albuterol with HFA propellants required a reengineering of the inhaler’s metering valves.11 With these modified valves, the HFA inhalers may need less frequent reprim-

### Table 2. Short-Acting β-Agonists Approved for Treatment of Asthma and COPD and Available in the United States as Metered-Dose Inhalers.10

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Size of Inhaler</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CFC-containing products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to be withdrawn by the end of 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol base</td>
<td>Generic</td>
<td>Armstrong</td>
<td>90</td>
<td>200</td>
<td>Contains oleic acid; prime after 4 days‡‡</td>
</tr>
<tr>
<td><strong>CFC-containing products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to be withdrawn in the future</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol–ipratropium</td>
<td>CombiJet</td>
<td>Boehringer Ingelheim</td>
<td>90 (albuterol), 18 (ipratropium)</td>
<td>200</td>
<td>Contains soya lecithin</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Primatene Mist</td>
<td>Wyeth Consumer Healthcare</td>
<td>220</td>
<td>270 and 405</td>
<td>Nonprescription</td>
</tr>
<tr>
<td>Metaproterenol sulfate</td>
<td>Alupent</td>
<td>Boehringer Ingelheim</td>
<td>650</td>
<td>100 and 200</td>
<td></td>
</tr>
<tr>
<td>Pirbuterol acetate</td>
<td>Maxair Autohaler</td>
<td>3M Pharmaceuticals</td>
<td>200</td>
<td>400</td>
<td>Breath-actuated inhaler</td>
</tr>
<tr>
<td><strong>HFA replacements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol sulfate</td>
<td>ProAir HFA</td>
<td>IVAX</td>
<td>90 (base)</td>
<td>200</td>
<td>Contains ethanol; prime after 2 weeks‡‡</td>
</tr>
<tr>
<td></td>
<td>Proventil HFA</td>
<td>Schering-Plough</td>
<td>90 (base)</td>
<td>200</td>
<td>Contains ethanol and oleic acid; prime after 2 weeks‡‡</td>
</tr>
<tr>
<td></td>
<td>Ventolin HFA</td>
<td>GlaxoSmithKline</td>
<td>90 (base)</td>
<td>200</td>
<td>Does not contain excipients; prime after 2 weeks‡‡; discard 2 months after removing from pouch</td>
</tr>
<tr>
<td></td>
<td>Levalbuterol tartrate</td>
<td>Xopenex HFA</td>
<td>45 (base)</td>
<td>200</td>
<td>Contains ethanol and oleic acid; prime after 3 days‡‡</td>
</tr>
</tbody>
</table>

* Data are from the Food and Drug Administration, Center for Drug Evaluation and Research.10
† These products are not included in the April 4, 2005, “Final Rule”3 on removal of essential-use designations but will be subject to withdrawal in the future.
‡ Prime by firing four puffs into the air before the first use and when there has been no use for the indicated period.
ing (i.e., the firing of the unit to load the metering valve) than the CFC inhalers, although the frequency with which repriming is required varies among the HFA products (Table 2).²⁶ All albuterol inhalers contain more doses than indicated on the label. When the label amount is exceeded, however, CFC inhalers deliver inconsistent amounts of albuterol (i.e., there is an erratic tailing off in the dose delivered). With the reengineered HFA inhalers, puffs delivered beyond the labeled amount may contain more albuterol, but the tail-off may be more abrupt (with puffs delivering doses close to the indicated amount of drug followed by puffs that deliver nothing).²⁷

**Efficacy and Safety of HFA Inhalers**

HFA albuterol inhalers have been evaluated in controlled clinical trials involving children²⁸-³⁰ and adults³¹-³⁸ with asthma, mainly in comparison with CFC albuterol inhalers (Table B in the Supplementary Appendix). To our knowledge, no published data from studies of the use of HFA albuterol inhalers by patients with COPD are available. In dose-ranging studies, two puffs of HFA albuterol resulted in significantly greater bronchodilatation than did placebo, and increases in the forced expiratory volume in 1 second (FEV₁) were similar to those with CFC albuterol.³¹,³² These effects were maintained with regular use of HFA albuterol for 2 to 4 weeks in children²⁹,³⁰ and for 12 weeks in adults.³⁷,³⁸

Studies of the effect of cumulative doses of CFC albuterol and HFA albuterol provide insight into what might be expected when patients use their albuterol inhaler repeatedly because of incomplete relief. These studies, in which 16 puffs of albuterol were administered over a period of approximately 2 hours, showed that after 8 cumulative puffs, the change in FEV₁ tended to plateau, with no significant differences in bronchodilating effects found between CFC and HFA inhalers (Fig. 2).³⁵,³⁶ Although the cumulative-dose studies suggest that differences in spray characteristics between the HFA and CFC albuterol inhalers are not clinically apparent even at high doses, use of bronchodilatation as a pharmacodynamic end point is limited. With higher doses, there is a trend toward more systemic β₂-agonist effects — specifically, tachycardia (Fig. 2) and hypokalemia — with the HFA formulation.³⁵,³⁶

A pharmacodynamic approach to assessing inhaled albuterol products has been developed that is based on protection against laboratory-induced bronchoconstriction.³⁹,⁴⁰ Parameswaran et al.
found that HFA albuterol and CFC albuterol were equipotent in providing protection from methacholine-induced bronchoconstriction (Fig. 3). In children and adults, two puffs of HFA albuterol 30 minutes before an exercise challenge has also been shown to provide protection from exercise-induced bronchospasm that is significantly greater than that provided by placebo and similar to that provided by CFC albuterol.

An extensive preclinical toxicology program demonstrated that HFA-134a has a favorable safety profile. Self-administration of HFA propellant by normal subjects for 28 days was associated with fewer adverse events than the same use of CFC propellant. Use of an HFA placebo (an inhaler with HFA but without albuterol) in clinical trials for up to 12 weeks was not associated with unusual adverse events. Adverse events reported more commonly with HFA albuterol than with placebo are similar in frequency to those reported with CFC albuterol (Table 3). In cumulative-dose studies, tremor, nervousness, and headache were dose-related. Patients who switch from CFC albuterol to HFA albuterol have similar patterns of reported adverse events with the two formulations, and there is no evidence of loss of asthma control after the switch. Abnormal results of laboratory tests have not been associated with HFA albuterol when used in recommended doses.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>HFA Albuterol</th>
<th>CFC Albuterol</th>
<th>HFA Placebo</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation sensation</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Taste sensation</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions or symptoms</td>
<td>6</td>
<td>4</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>3–5</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>Not reported</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>Not reported</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3–7</td>
<td>2</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Mental status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>7</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear, nose, and throat irritation</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5–16</td>
<td>22</td>
<td>2–14</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>21</td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5–14</td>
<td>5</td>
<td>2–9</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* Data include all adverse events (whether or not they were considered by the investigator to be drug-related) that occurred at a rate of at least 3% in the group treated with HFA albuterol and that occurred with greater frequency than in the placebo group. Data are from randomized, double-blind, parallel studies of 1347 adolescents and adults who received HFA albuterol, CFC albuterol, or HFA placebo (two puffs four times a day) for 6 to 12 weeks. Data were compiled from the adverse-reaction sections of the package inserts for ProAir HFA, Proventil HFA, and Ventolin HFA. Adverse events in 2-to-4-week studies of children less than 12 years old occurred at a low incidence and were similar to those in the trials that involved adults.
Large post-marketing surveillance studies have not described serious adverse events with regular use of HFA albuterol and have shown no increase in hospitalization rates for respiratory problems with HFA albuterol as compared with CFC albuterol.

**ECONOMIC EFFECT OF THE TRANSITION TO HFA INHALERS**

Because the formulation patents for HFA products extend into the next decade, the withdrawal of CFC albuterol inhalers from the U.S. market will eliminate generic albuterol inhalers. Generic CFC albuterol inhalers are currently much less expensive than brand-name albuterol inhalers (CFC or HFA), and a complete transition to HFA albuterol may increase U.S. health care costs by as much as $1.2 billion annually until a generic HFA product becomes available. Whereas patients paying out of pocket will be particularly vulnerable to these cost increases, even for patients with a prescription benefit plan, the copayment may increase because HFA products are branded. For instance, prescription audit data from 2004 indicate that the weighted average price paid in retail pharmacies across all payer types (self-pay, third-party, and Medicaid) was $13.50 for generic CFC inhalers and $39.50 for HFA inhalers. To save money, patients may turn to less expensive alternatives, such as nonprescription epinephrine inhalers or a metaproterenol inhaler that is less β₂-selective.

Although many pharmaceutical companies have financial-assistance programs for uninsured, lower-income patients, the effect of the transition to HFA inhalers on these patients is uncertain.

**REFERENCES**


**CONCLUSIONS**

The successful implementation of the Montreal Protocol worldwide has reduced CFC production, and stratospheric ozone levels have begun to recover. The reduced availability of CFCs has been a challenge to the pharmaceutical industry in its efforts to ensure the future supply of a range of inhaled medications for the millions of patients with asthma and COPD who depend on these treatments, including treatment with albuterol. Several reengineered albuterol inhalers that use HFAs in place of CFCs as propellants have been developed and are now widely available on the U.S. market and worldwide. Clinical trials in children and adults with asthma have demonstrated that when these HFA albuterol products are administered at the FDA-approved dose, their efficacy and safety profiles are similar to those of the CFC albuterol products they are intended to replace. However, there are differences between HFA and CFC albuterol products and among the various HFA albuterol products, all of which should be discussed with patients as they move from CFC to HFA albuterol. The transition is well under way in the United States, but this transition will increase expenditures for albuterol metered-dose inhalers.

Dr. Colice reports receiving lecture fees from GlaxoSmithKline and consulting fees from IVAX/Teva and Schering-Plough. Dr. Hendeles reports receiving a research grant from GlaxoSmithKline and consulting fees from AstraZeneca. No other potential conflict of interest relevant to this article was reported.

Dr. Meyer’s participation in this article represents his personal views and does not necessarily represent the views of the FDA.

We thank C. Max Colice for his assistance with Figure 1.
46. Salat D, Popov D, Sykes AP. Equivalence of salbutamol 200 µg four times daily propelled by propellants 11 and 12 or HFA 134a in mild to moderate asthma. Respir Med 2000;94 Suppl B:S22-S28.
A healthy 9-year-old boy had a 1-year history of an itchy right eye with frequent tearing. Small masses that gradually developed in the right caruncula lacrimalis area were associated with intermittent, spontaneous minor bleeding. The ophthalmic examination showed diffuse, multifocal small nodules with papillomatous growth and vascular fronds. The upper and lower tarsal conjunctiva was also involved (Panel A). No warts were noted on the remainder of the physical examination. A histopathological examination of the ocular lesion revealed acanthotic conjunctival epithelial growth in a fingerlike pattern with central fibrovascular cores (Panel B). Koilocytosis, a nuclear pyknosis with cytoplasmic clearing, was occasionally seen (Panel B, arrowhead). The findings were consistent with the presence of viral papilloma. The various serotypes of human papillomavirus infection are considered to be causes of this condition. This type of lesion may resolve spontaneously. Although several excisions were performed in this case, the papilloma recurred.

Copyright © 2007 Massachusetts Medical Society.
A 55-year-old man was admitted to this hospital after being impaled by the prow of a racing shell in a rowing accident.

The patient, who was in excellent health, was sculling on the Charles River in Boston when his boat collided head-on at approximately 7:20 a.m. with an eight-person shell moving in the opposite direction; both boats were estimated to be traveling at 24 to 32 km per hour. The initial contact between the vessels tore a rubber safety bumper from the larger boat, and the sharp prow of the larger craft entered the left side of the patient's lower back, above the iliac crest, and exited the central portion of his lower abdomen above the pubis (Fig. 1). He then slipped off the larger vessel's prow and fell into the water. He did not lose consciousness and within 5 minutes was pulled from the water by the occupants of the larger boat and brought to shore. Emergency medical services (EMS) were called and were dispatched at 7:23 a.m., arriving at 7:36.

On examination by EMS personnel, the patient was alert, in pain, and lying on his right side. The systolic blood pressure was palpable at 108 mm Hg, the diastolic pressure was not recorded, and the pulse was 72 beats per minute; the respirations were 16 breaths per minute. Capillary return was less than 2 seconds. The skin was cool and wet; the lungs were clear. There were lacerations on the lower back and abdomen, with loops of intestine protruding from the wounds. Oxygen was administered by face mask, and the patient was transferred by ambulance to the emergency department of this hospital, departing the scene at 7:44 a.m. While in transit, an intravenous line was placed, and 300 ml of normal saline was rapidly infused. The trauma center of this hospital was notified at 7:52, and the ambulance arrived at the hospital at 7:55.

The patient had a history of obstructive sleep apnea, a laparoscopic cholecystectomy, lumbar spinal fusion, tonsillectomy, and adenoidectomy. He had no allergies to medications. He was married, exercised regularly, and took no medications. He drank alcohol in moderation and did not smoke or use illicit drugs.

The patient arrived at the trauma resuscitation area at 7:58 a.m., where he was met by the trauma team, members of which arrived between 7:55 and 8:10. The radiology service, clinical laboratories, blood bank, and operating room were alerted.
On arrival, the patient was alert. The blood pressure was 120/60 mm Hg, the pulse 78 beats per minute, and the rectal temperature 36.1°C; the respirations were 28 breaths per minute while the patient was breathing 100% oxygen with a non-rebreathing mask. The skin was cool and pale; carotid, femoral, and pedal pulses were 2+ bilaterally. There was a horizontal laceration

Figure 1. Diagram of the Patient’s Injury.
Two boats traveling in opposite directions (top) collided. The bumper on the prow of the eight-person shell (inset) was knocked off by the impact. The sharp prow of the boat entered the left flank and exited through the left lower abdomen. A loop of intestine was forced out of the abdomen by the impact. The small and large bowels were lacerated, but the ureters and spleen were not injured.
in the left lower abdominal quadrant that was 10 cm in length and a laceration on the posterior left flank that was approximately 14 cm in length (Fig. 2A and 2B). Loops of small bowel protruded from both wounds, with vigorous bleeding. Rectal examination was normal, and there was no blood in the rectum. There was no clinical evidence of injury to the spine, and the results of the remainder of the examination were normal.

Results of laboratory tests are shown in Table 1. The patient was placed on a warm blanket, and a urinary catheter was inserted; the urine was yellow and cloudy, with more than 100 red cells per high-power field. The trachea was intubated after the administration of fentanyl at 8:07 a.m. A chest radiograph was normal. A central venous line was placed, and warm crystalloid solution was infused. Tetanus toxoid was administered intramuscularly, and ampicillin and metronidazole were administered intravenously. The blood pressure rose to 140/77 mm Hg. The patient was taken to the operating room at 8:22.

General endotracheal anesthesia was induced with isoflurane and propofol. Intraoperative radiographs revealed the previous vertebral laminectomy at L5–S1 and a comminuted fracture of the left ilium extending close to the left sacroiliac joint (Fig. 3A). The patient was placed in a semilateral position to allow access to both wounds. The neck, torso, and thighs were prepped and draped. Blood and crystalloid solution were infused. The posterior wound was briefly examined, a fragment of bone from the iliac crest was removed, and the wound was packed so that the laparotomy could proceed. A midline abdominal incision was made. Exploration of the abdomen disclosed avulsion of approximately 60 cm of small intestine, with several full-thickness lacerations, and avulsion of the left colon, with multiple contusions (Fig. 2C). The peritoneal cavity contained intestinal contents, fragments of muscle, wood, flecks of paint, and fluid that was presumed to be river water. There was vigorous bleeding from mesenteric vessels.

Bleeding was controlled, followed by resection and primary anastomosis of the injured segments of the intestine and irrigation of the abdominal cavity and retroperitoneum with warmed crystalloid solution. The other abdominal organs, kidneys, ureters, and major nerves appeared to be intact. The anterior wound in the abdominal wall was débrided, foreign material and muscle fragments were removed, and the wound was closed. To assess the extent of muscle damage, an incision was made in the skin to connect the entry and exit wounds. The wound in the lower back
Table 1. Results of Hematologic and Serum Chemical Laboratory Tests.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range, Adults†</th>
<th>On Admission</th>
<th>Second Hospital Day</th>
<th>Third Hospital Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (in males)</td>
<td>42.5</td>
<td>27.6</td>
<td>21.9</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (in males)</td>
<td>14.9</td>
<td>9.4</td>
<td>7.6</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4,500–11,000</td>
<td>9,800</td>
<td>10,300</td>
<td>10,100</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (per mm³)</td>
<td>40–70</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (per mm³)</td>
<td>22–44</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes (per mm³)</td>
<td>4–11</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils (per mm³)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–350,000</td>
<td>306,000</td>
<td>212,000</td>
<td>190,000</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>11.1–13.1</td>
<td>13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial-thromboplastin time (sec)</td>
<td>22.1–35.1</td>
<td>24.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>75–115</td>
<td>210</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>136–145</td>
<td>136</td>
<td>138</td>
<td>138</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>3.5–5.0</td>
<td>3.5</td>
<td>4.5</td>
<td>4.5</td>
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<tr>
<td>Chloride (mmol/liter)</td>
<td>98–106</td>
<td>106</td>
<td>103</td>
<td>103</td>
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<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>21–30</td>
<td>25.9</td>
<td>28.9</td>
<td>30.7</td>
</tr>
<tr>
<td>Urea nitrogen (mg/dl)</td>
<td>10–20</td>
<td>19</td>
<td>16</td>
<td>14</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>&lt;1.5</td>
<td>1.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.3–1.0</td>
<td>2.0</td>
<td>2.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Direct</td>
<td>0.1–0.3</td>
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<td>0.7</td>
<td>0.9</td>
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<tr>
<td>Protein (g/dl)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.5–8.0</td>
<td>6.5</td>
<td>4.8</td>
<td></td>
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<tr>
<td>Albumin</td>
<td>3.5–5.5</td>
<td>3.8</td>
<td>2.7</td>
<td></td>
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<tr>
<td>Globulin</td>
<td>2.0–3.5</td>
<td>2.7</td>
<td>2.1</td>
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<tr>
<td>Phosphorus (mg/dl)</td>
<td>3–4.5</td>
<td>2.1</td>
<td>2.9</td>
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<tr>
<td>Magnesium (mg/dl)</td>
<td>0.9–1.5</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
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<tr>
<td>Calcium (mg/dl)</td>
<td>9.0–10.5</td>
<td>8.8</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (U/liter)</td>
<td>60–400 (in males)</td>
<td>331</td>
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<tr>
<td>Creatine kinase isoenzymes (ng/ml)</td>
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<td>Alkaline phosphatase (U/liter)</td>
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<td>Aspartate aminotransferase (U/liter)</td>
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<tr>
<td>Alanine aminotransferase (U/liter)</td>
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<td>51</td>
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<tr>
<td>Lipase (U/dl)</td>
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<tr>
<td>Amylase (U/liter)</td>
<td>60–180</td>
<td>87</td>
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* To convert the values for glucose to millimoles per liter, multiply by 0.05551. 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 magnesium to milliequivalents per liter, multiply by 0.5. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for total and direct bilirubin to micromoles per liter, multiply by 17.1.

† 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 who do not have medical conditions that could affect the results. These ranges may therefore not be appropriate for all patients.
was examined; fragments of wood and necrotic muscle were removed, the wound was irrigated, and the retroperitoneum was closed behind the bowel. Lumbar nerve roots appeared to be stretched, and one was completely divided within the wound. Primary closure of the entire defect in the muscle was not possible, so a vacuum sponge was inserted, and the skin closed.

Pathological examination of the excised tissue revealed a segment of small bowel, 19.5 cm in length, with two transmural lacerations that were 6.0 by 2.0 cm and 2.5 by 0.5 cm, and a segment of the colon, 6.0 cm in length, with a serosal injury that was 1.5 by 0.8 by 0.2 cm.

Postoperatively, the patient was placed on bed rest with nasogastric suctioning and no oral intake. Ampicillin, levofloxacin, and metronidazole were administered intravenously. Narcotic analgesics and dalteparin were given. On the second hospital day, radiographs and computed tomographic (CT) scanning of the pelvis confirmed the presence of a fracture through the wing of the left ilium, with a slight posterior displacement of the iliac wing that did not enter the acetabulum (Fig. 3B).

On the third hospital day, 2 units of packed red cells were transfused. The patient was returned to the operating room, and the posterior wound was reassessed. No necrotic tissue or purulent drainage was found. A defect in the soft tissues forming the posterior abdominal wall was continuous with a triangular defect in the pelvic brim left by the prow of the boat, into which a loop of bowel had herniated (Fig. 3C). A local fascial flap was rotated into the defect to close it, and the flap was secured to the pelvis with sutures.

During the next week, the patient gradually advanced to ambulation, and the nasogastric tube was removed; oral intake was resumed, and solid foods were gradually introduced. On the eighth hospital day, the posterior drain came out and was not replaced; the next day, intravenous antibiotics were discontinued, and oral antibiotics were administered. On the 10th hospital day, the maximum temperature was 37.4°C; the abdominal incisions were clean, dry, and intact; and the abdomen was soft, not distended, and mildly tender, with bowel sounds present.

The patient was discharged to his home.

Figure 3. Radiographic Images.

An anteroposterior radiograph of the pelvis obtained with portable equipment (Panel A) reveals a vertical fracture of the left iliac crest (arrows). A dislodged fracture fragment (arrowhead) projects over the left ilium. Gas is present in the soft tissues adjacent to the fracture. A three-dimensional anteroposterior computed tomographic (CT) reformation of the bony pelvis (Panel B) shows the fracture lateral to the left sacroiliac joint. The left acetabulum, left sacroiliac joint, and superior and inferior pubic rami are shown to be intact. A postoperative axial CT slice through the top of the iliac crests viewed in soft-tissue windows (Panel C) shows bowel at the fracture site (inside circle), a finding consistent with lumbar bowel herniation through the fracture. Free intraperitoneal air is present (arrowheads).
**DISCUSSION OF MANAGEMENT**

Dr. Richard Sacknoff: An anteroposterior radiograph of the pelvis obtained with portable equipment before surgery (Fig. 3A) shows a vertical fracture through the left iliac crest. At the top of the iliac crest, there is a V-shaped defect, which was probably caused by the direct penetration of the prow. Adjacent to this is a large bone fragment. Gas in the soft tissues adjacent to the fracture site is consistent with the presence of an open wound.

A CT scan of the pelvis obtained on the second hospital day without the oral or intravenous administration of contrast material confirms that the left iliac fracture is stable, and the sacroiliac joints, left acetabulum, and pubic rami are intact. These findings are well visualized on a three-dimensional anteroposterior coronal reformation (Fig. 3B). Also present is a left transverse process fracture of L5.

An axial CT slice viewed in soft-tissue windows (Fig. 3C) at the level of the top of the iliac crests shows the presence of bowel at the fracture site, which probably represents a lumbar hernia, although this is difficult to see without orally administered contrast material.

**TRAUMA RESUSCITATION AND ABDOMINAL OPERATIVE ISSUES**

Dr. Robert L. Sheridan: The principles of initial evaluation and resuscitation of patients with trauma are well illustrated in this case. The patient was identified in the field as seriously injured and was taken directly to a level 1 trauma center, where a team was activated while he was en route, with the members assembled in a properly equipped trauma receiving area within minutes after his arrival. In patients with trauma, immediate threats to life must be systematically identified and addressed. These principles are taught in the Advanced Trauma Life Support course of the American College of Surgeons and include initiating rapid evaluation and control of the airway, vascular access, and fluid resuscitation.

In this case, it was important to decide how soon to operate. The current generation of rapid, multidetector, helical CT scanners has rendered most exploratory operations undertaken for diagnostic purposes obsolete, except in hemodynamically unstable patients, particularly those with ongoing bleeding. In the majority of cases of blunt trauma, diagnostic radiology is the next step, once control of the airway and intravenous fluid resuscitation have been initiated. In this patient, with obvious rapid bleeding and evisceration, diagnostic radiographic procedures were not performed, and he was taken directly to the operating room.

Particularly in the absence of diagnostic radiographic imaging, the laparotomy for trauma should be conducted in a systematic fashion, so as not to miss any injuries. Operations should take place in a warm operating room, properly staffed by nurses and anesthesiologists with blood products and a wide range of intestinal and vascular instruments immediately available. In this case, the room was warmed to 32°C. Bleeding and fecal contamination must be stopped first. A systematic evaluation of the abdominal and retroperitoneal contents is then conducted to document all injuries. This evaluation should include examination of the entire gastrointestinal tract from the esophagus to the rectum, the liver and spleen, and all retroperitoneal structures, including the kidneys, pancreas, duodenum, and major vascular structures.

Next, depending on how stable the patient’s condition is, a decision must be made whether to perform immediate repair of identified injuries. If delayed repair (“damage control”) is a wiser option, the patient’s condition can be stabilized in the interim in the intensive care unit (ICU). In this patient, vigorous bleeding from the mesentery and retroperitoneum was stopped first, ongoing intestinal spillage was controlled temporarily with clamps, and the abdominal and retroperitoneal contents were then systematically examined. This patient’s condition seemed to be stable enough for the surgical team to proceed with immediate resection and anastomosis of the small bowel and colonic injuries. The operation was performed, and the rent in the lower abdomen was closed with local flaps.

**ORTHOPEDIC EVALUATION AND REHABILITATION**

Dr. R. Malcolm Smith: The initial evaluation of complex musculoskeletal injuries cannot be separated from the assessment of the whole trauma. In a case of blunt trauma, severe isolated or multiple orthopedic injuries often dominate the clinical presentation. Like injuries to other organ systems, orthopedic injuries can be life-threatening and of primary importance. Immediate involvement of the orthopedic trauma specialist has to be part of
any well-organized effort to manage trauma. In a patient who is hemodynamically stable, an initial orthopedic physical examination is performed during the secondary survey, after the initial assessment of the airway and circulation. Any immediately life- or limb-threatening problems, such as dislocations with vascular compromise, are addressed. This step is followed by a careful radiographic evaluation directed by the findings on physical examination.

In this case, the patient’s condition was too unstable for immediate orthopedic radiographic evaluation, and his initial orthopedic operative care was planned on the basis of the intraoperative findings and the primary pelvic radiograph. Before opening the abdomen, we explored the entrance wound. We found a direct penetrating injury to the left posterior flank, with a large entry wound just above the iliac crest and an anterior exit wound just above the inguinal ligament. There was a triangular defect in the iliac crest, with a fracture extending down to the pelvic brim, but the pelvic ring was intact. The triangular shape of the defect appeared to match the shape of the prow of the boat. This wound was packed to control bleeding so that the laparotomy could proceed.

At the conclusion of the abdominal portion of the surgery, devitalized soft-tissue and bony fragments were removed from the posterior wound. The injury had essentially created a traumatic lumbar hernia through a bony and soft-tissue defect. After débridement, this defect was loosely approximated and packed, and a delayed reconstruction was planned.

Although many surgeons would delay orthopedic reconstruction in severely injured patients, current data suggest that early skeletal stabilization followed by immediate soft-tissue reconstruction provides the best environment for healthy wound healing. We therefore performed a second procedure 2 days later, in which we reconstructed the soft tissue using fascial flaps rotated from the distal extent of the local erector spinae muscles and fascia; these flaps were secured to the edges of the bony defect with bony suture anchors (Fig. 3A and 3B). Additional coverage of the defect was obtained by incorporating some of the posterior elements of the internal oblique muscle and by releasing the origin of the gluteus maximus from the iliac crest posteriorly, which allowed proximal rotation of part of the muscle. After appropriate initial recovery, the patient was allowed to walk with crutches for support, using the touch-down, weight-bearing method. The program of rehabilitation was advanced as his comfort allowed, with weight-bearing activity as tolerated after a few weeks.

At a follow-up office visit, the patient reported good early progress; 3 months after discharge he was walking, with no specific restrictions in activity. He had noted the change in the contour of his buttock, but there was no evidence of a hernia. Six months after discharge, he had a feeling of aching, stiffness, and tightness over the back of his pelvis where the injury took place, but he was back to rowing and was fully active.

TRAUMA SYSTEMS AND TRAUMA CENTERS
Dr. George Velmahos: This patient’s survival depended on the existence of a functioning trauma system; these systems can decrease mortality by 15% and preventable mortality by 50%. The level 1 trauma center is a tertiary care facility that can cover every aspect of care for the injured patient, conduct clinically significant research, train the new generation of health care providers, establish meaningful prevention programs, and communicate with the surrounding community. Trauma centers are recertified every 3 years by the American College of Surgeons, which also maintains a database to monitor outcomes (see the American College of Surgeons National Trauma Data Bank at www.facs.org/trauma/ntdb.html).

This patient was evaluated shortly after the accident (before his arrival at the hospital) by health care providers with protocols that included airway assessment, circulatory support, and spinal stabilization. Statewide protocols also dictated the level of trauma center needed, based on the severity of the injuries. Within minutes, the patient was transported to the closest level 1 trauma center; during transport, the hospital was alerted to expect the patient. On notification, the trauma team, including trauma surgeons, emergency room physicians, orthopedic surgeons, anesthesiologists, respiratory therapists, and nurses, was activated and assembled in the emergency room. A member of the trauma team from each discipline is on duty in the hospital at all times; team members are contacted through a group paging system and respond to three tiers of urgency (“stat,” “urgent,” and “consult,” with “stat” being the most critical). A response time of 3 to 6 minutes, as in
this case, is expected. Also in this case, an operating room and a bed in the ICU were prepared in case of need. The emergency radiology department and blood bank were on standby. When the patient arrived, care was delivered in a rapid, organized, and systematic fashion. Protocols facilitated the process of care, functioning as guides and safeguards in stressful circumstances during which urgent decision making was required.

Dr. Sheridan: The patient was highly motivated to recover and worked avidly in physical therapy. He has since returned to competitive rowing.

Dr. Jay J. Schnitzer (Pediatric Surgical Service): How generalizable are these lessons? Are there other types of cases that would benefit from a similar system of management?

Dr. Velmahos: The lessons learned from organizing trauma systems are relevant to nontrauma emergency care. A 70-year-old patient with a perforated diverticulum is as sick or sicker than a young patient with a perforated colon from a gunshot wound. There is no organized system for treating the former, whereas the latter receives the benefits of the entire trauma system. The American College of Surgeons is developing a concept of acute care surgery that is based on the principle of trauma management.

Dr. Nancy Lee Harris (Pathology): The system of care in place in many states for patients who have had strokes adheres to principles similar to those of the trauma system approach.9

ANATOMICAL DIAGNOSIS

Traumatic lacerations of the abdominal wall and viscera, with pelvic fracture.

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

REFERENCES

The age-adjusted rate of death from breast cancer in the United States was 24% lower in 2003 than it was in 1989, a decline that has been attributed principally to both the role of mammography in detecting early-stage tumors and improvements in therapy. Indeed, early diagnosis and therapy have been the cornerstone of efforts to control breast cancer, since a readily accessible preventive strategy for women with an average risk has been elusive. Prevention is clearly the preferable strategy for controlling cancer, but for the foreseeable future, the control of breast cancer will depend mostly on early detection, careful diagnostic evaluation, and therapy.

The introduction and widespread use of mammography for the early detection of breast cancer is one of the most important recent achievements in the control of cancer. The prognostic value of detecting breast cancer while it is still localized to the breast exceeds what can be achieved with therapy when breast cancer is advanced, and over the past decade the trend toward a more favorable stage at diagnosis has played a major role in the reduction of the rate of death due to breast cancer. Although the association is difficult to measure, it is likely that ultrasonography, magnetic resonance imaging (MRI), and digital mammography also improve the outcome when they are used as a substitute for or adjunct to conventional film mammography for women in whom conventional mammographic screening has not been useful. For example, digital mammography has recently been shown to be a more effective imaging tool in younger women and in women with heterogeneously or extremely dense breasts. It is well established that conventional film mammography does not identify all breast cancers, and these other imaging methods can detect tumors that are occult on mammography or can provide more information about findings that were inconclusive with conventional imaging.

Once breast cancer has been detected, the importance of thorough and accurate breast imaging is paramount, because multicentric breast cancer may preclude breast-conserving strategies, and the detection of a synchronous, contralateral primary tumor may affect choices regarding surgery and reconstruction. The risk of local recurrence is a dark cloud that hangs over patients with newly diagnosed breast cancer and longer-term survivors, despite reassurances that multicentric or multifocal disease that may be present, but not visible, can be effectively treated by whole-breast irradiation and adjuvant therapy. Even with this reassurance, it is likely that most women would prefer the detection of such mammographically invisible lesions so that they could be factored into decision making with regard to treatment. For this reason, a growing proportion of patients with newly diagnosed breast cancer are undergoing further evaluation with MRI.

In this issue of the Journal, Lehman and colleagues report the results of their study of the effectiveness of MRI in the detection of cancer in the contralateral breast after negative clinical and mammographic findings in women with newly diagnosed breast cancer. The follow-up period was long enough to permit an estimate of conventional measures of test performance, including the sensitivity, specificity, area under the receiver-operating-characteristic curve, and positive and negative predictive values. Among 969 study participants, MRI of the contralateral breast was performed within 60 days after the diagnosis of...
unilateral breast cancer and within 90 days after clinical and mammographic breast examination showed normal findings.

Among 33 patients in whom breast tumors were diagnosed in the contralateral breast during the 12-month follow-up period, 30 tumors (invasive tumors in 18 women and ductal carcinoma in situ in 12) were detected by means of MRI. Thus, the additional diagnostic yield of MRI was 3.1% after negative findings on mammographic and clinical breast examination, with 91% sensitivity and 88% specificity. Although this specificity is lower than that which would generally be acceptable in a screening program, it is likely to be acceptable to women with unilateral breast cancer, since they will place a high priority on a thorough evaluation for the presence of other primary lesions. As Lehman and colleagues note, the very high negative predictive value of MRI can be reassuring to women whose concern about the presence of undetected disease leads them to seek prophylactic mastectomy of the contralateral breast. The authors also note the advantage of treating synchronous cancers simultaneously, thus avoiding another round of therapy at a later time when the tumor in the contralateral breast would be detected by means of conventional imaging or on the basis of symptoms. There may be arguments that the added sensitivity of MRI of the contralateral breast comes at high cost in terms of false positive results and overdiagnosis due to the high rate of detection of ductal carcinoma in situ. Nevertheless, the false positive rate and the predictive value of a positive test are in an acceptable range, and there is little persuasive evidence that most cases of ductal carcinoma in situ are not progressive. Therefore, there is value in detecting and treating malignant tumors in the contralateral breast that were not identified by means of mammography and clinical breast examination.

The responsible use of MRI for the evaluation of the breast is focused primarily on patients with a high probability of breast cancer, and it includes screening in women who are known or likely carriers of a BRCA1 or BRCA2 mutation. The American College of Radiology's practice guideline for the performance of breast MRI outlines 12 clinical applications of MRI in the evaluation of breast disease.9 Coincident with this issue of the Journal, the American Cancer Society is publishing new recommendations for breast-cancer screening in women at high risk for breast cancer.10 In the 2003 update to its guideline for breast-cancer screening, the American Cancer Society stated that women at increased risk for breast cancer might benefit from the earlier initiation of screening, shorter screening intervals, or the addition of screening methods such as breast ultrasound or MRI.11 On the basis of newer evidence, as well as requests from clinicians for greater guidance in the use of breast MRI, the guideline now recommends annual breast-cancer screening by means of MRI for women with approximately 20% or greater lifetime risk of breast cancer, according to risk models that are largely dependent on a strong family history of breast or ovarian cancer. Annual MRI screening is also recommended for women who have undergone radiotherapy to the chest for Hodgkin's disease.12 The updated guideline also states that there is insufficient evidence to make a recommendation for or against MRI screening in women with a personal history of breast cancer, carcinoma in situ, or atypical hyperplasia or in women with extremely dense breasts.

Although breast MRI is not available in every clinical setting, its availability is increasing. In a recent national survey of 575 U.S. breast-imaging practices from the membership database of the Society of Breast Imaging, 12% of practices reported that they offer breast-cancer screening with MRI, and 51% reported offering diagnostic evaluation with MRI.13 However, there have been concerns about the increasing use of breast MRI and the wide-ranging quality of the examinations. It is unclear whether the results reported by Lehman and colleagues could be reproduced in all centers offering MRI today. Of particular concern are facilities that perform breast MRI but lack the ability to perform biopsies. Patients at such facilities who require follow-up evaluation at a center with the capacity to perform a biopsy in effect have to undergo a repeat of the entire imaging procedure. The new American Cancer Society guidelines strongly recommend that breast MRI not be performed in the absence of the capacity to perform biopsies.

This year, the American College of Radiology is likely to initiate a voluntary accreditation program for breast MRI that is similar to its current programs for mammography and breast ultrasonography. Participation in the new program will probably be greater than that for mammography before the passage in 1992 of the Mammog-
Impact in Atherosclerotic Events (ILLUMINATE)
The Food and Drug Administration, the Investigative New Drug (IND), and a large clinical trial. As reported by Pfizer to raise HDL cholesterol levels, it recently failed though the CETP inhibitor torcetrapib is effective of drugs that inhibit CETP was developed.

Plasma levels of high-density lipoprotein (HDL) cholesterol are inversely related to the incidence of coronary heart disease and stroke. The lowering of low-density lipoprotein (LDL) cholesterol with statin therapy reduces the risk of atherosclerotic cardiovascular disease but only by about one third. These findings have led to the idea that raising HDL cholesterol might be a treatment for atherosclerosis. On the basis of the high-HDL phenotype of a human genetic deficiency of cholesterol ester transfer protein (CETP),\(^1\) a new class of drugs that inhibit CETP was developed.\(^2\) Although the CETP inhibitor torcetrapib is effective at raising HDL cholesterol levels, it recently failed in a large clinical trial. As reported by Pfizer to the Food and Drug Administration, the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) study involving 15,000 patients at high risk for coronary heart disease was stopped prematurely, after a little more than a year, because of an excess of deaths, myocardial infarction, angina, revascularization procedures, and heart failure in patients receiving torcetrapib plus atorvastatin, as compared with those receiving atorvastatin alone.\(^3\)

In this issue of the Journal, Nissen et al. report on an independent, parallel study, called the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial (ClinicalTrials.gov number, NCT00134173),\(^4\) which evaluated the effect of torcetrapib–atorvastatin therapy versus atorvastatin alone on atherosclerotic burden in coronary arteries, using intravascular ultrasonography to image plaque.

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The somewhat surprising outcome of the trial was that there was no significant difference in the primary end point assessing atherosclerotic plaque burden in the two study groups. Thus, the adverse clinical outcome of the ILLUMINATE trial cannot be readily attributed to a worsening of atherosclerotic plaque burden in the coronary arteries. Alternative explanations need to be sought. One possible reason is off-target toxic effects of torcetrapib. In the ILLUSTRATE trial, torcetrapib was associated with an increase of 4.6 mm Hg in mean systolic blood pressure, a greater rise than that seen during phase 2 development of this drug. The hypertensive effect of torcetrapib is probably not related to the drug’s mechanism, since such an effect is not seen in patients with a genetic CETP deficiency; in addition, other classes of CETP inhibitors do not cause this side effect. Although the increase in blood pressure seems modest, it may be indicative of an underlying adverse effect of torcetrapib, such as activation of the renin–angiotensin system or vasospasm. Though not apparent in studies of human genetic deficiency, CETP inhibition could also have detrimental effects on the vasculature that do not involve a change in buildup of atherosclerotic plaque. Further detailed analysis of the ILLUMINATE trial may be helpful in defining the relevant mechanisms.

The primary end point in the ILLUSTRATE trial — the change in percent atheroma volume — did not show significant improvement in patients receiving torcetrapib. However, an analysis of secondary end points provides a hint of possible benefit. There was a significant improvement in the total atheroma volume in patients in the torcetrapib–atorvastatin group, as compared with those in the atorvastatin-only group, and a trend toward improvement in another secondary end point, the volume of plaque in the most diseased coronary-artery segment. The decrease in plaque volume in the torcetrapib–atorvastatin group was small but represented a reduction of 50% more than that in the atorvastatin-only group. The fact that the change in plaque volume was larger than the change in percent atheroma volume (the percentage of total vessel volume occupied by plaque) could suggest that a decrease in atheroma volume was offset by an overall shrinkage of the vessel. Unfortunately, intravascular ultrasonography did not provide any information on the stability or thrombogenic potential of plaques.

Given that patients in the torcetrapib–atorvastatin group had a relative decrease of 20% in LDL cholesterol levels and a relative increase of 61% in HDL cholesterol levels, as compared with patients in the atorvastatin-only group, one would have expected more substantial improvements in coronary atheroma burden. Why was this not seen? One possibility is that off-target toxic effects of torcetrapib had an adverse effect on plaque volume. Another is that the HDL particles produced by CETP inhibition may be dysfunctional. HDL is thought to mediate a process of reverse cholesterol transport (i.e., removal of cholesterol from cells in the artery wall, transport through plasma, uptake in the liver, and excretion into bile). CETP mediates the transfer of cholesteryl ester from HDL to triglyceride-rich lipoproteins, which are subsequently cleared by LDL receptors in the liver. Thus, CETP has a central role in reverse cholesterol transport. When CETP is inhibited or deficient, direct hepatic clearance pathways for HDL cholesterol take over. The net result is a decrease in the fractional clearance of HDL from plasma but no change in the absolute clearance rate and no change in fecal elimination of sterols. Thus, inhibition of CETP is unlikely to result in an improvement in the overall process of reverse cholesterol transport. This lack of improvement may not matter, because the key step in reverse cholesterol transport from the point of view of atherosclerosis may be the removal of cholesterol from macrophage foam cells in the artery wall by HDL.

The efficiency of cholesterol efflux from arterial cells is probably determined by the concentration and functionality of HDL. Several different pathways of cellular cholesterol efflux have been described. (See Fig. 3 in the article by Nissen et al.) One of these pathways involves the release of lipid-poor apolipoprotein A-I from HDL and cholesterol efflux through the ATP-binding cassette transporter A1 (ABCA1) expressed in macrophages. The continued release of apolipoprotein A-I from HDL may depend on a cycle of CETP-mediated exchange of cholesteryl ester in HDL for triglycerides in very-low-density-lipoprotein (VLDL) followed by lipase action on HDL and release of lipid-poor apolipoprotein A-I. Inhibition of CETP is unlikely to favor this pathway. However, HDL also promotes cholesterol efflux from foam cells by mechanisms independent of ABCA1.
A second pathway involves another ATP-binding cassette transporter, G1 (ABCG1), and leads to the release of macrophage cholesterol onto HDL particles. The drive for this pathway appears to depend on ongoing cholesterol esterification mediated by the action of lecithin–cholesterol acyltransferase (LCAT) on HDL and is favored by the presence of apolipoprotein E in HDL. Although large HDL particles from patients with a homozygous CETP deficiency have a high content of LCAT and apolipoprotein E and show substantially enhanced cholesterol efflux from macrophages, recent studies in patients treated with 60 mg of torcetrapib daily (the dose used in the ILLUSTRATE and ILLUMINATE trials) indicated only modest improvements in these measures, although a higher dose of the drug had a more pronounced effect. Thus, it is possible that partial inhibition of CETP by 60 mg of torcetrapib did not capture the optimal changes in HDL. In addition to cholesterol efflux, HDL has antioxidant and antiinflammatory properties. A recent analysis of the proteome of HDL has revealed a plethora of low-abundance components that could potentially regulate the activity of thrombotic, inflammatory, and complement systems. The relevance of these pleiotropic properties of HDL to its atheroprotective functions is unknown, but such actions could have been adversely affected by CETP inhibition.

In summary, although findings of the clinical and coronary-imaging studies involving torcetrapib are disappointing, it is likely that at least part of the adverse effects were caused by nonmechanism-related toxicity of this particular drug. There was no evidence that CETP inhibition actually worsens atherosclerotic plaque burden, and there was even some improvement in a secondary measure of plaque volume. This finding suggests modest regression of plaque and provides a glimmer of hope for the future development of this class of drugs. Although the lowering of LDL cholesterol by CETP inhibition is likely to be antiatherogenic, it still needs to be shown that an increase in HDL levels by this mechanism is beneficial. A deeper understanding of the different functions of HDL and their associated biomarkers is badly needed. It would seem reasonable to proceed with caution in studies of other classes of CETP inhibitors that do not cause hypertension, while monitoring for potential adverse effects on vascular function. When used in combination with clinical trials, imaging studies such as intravascular or carotid ultrasonography to assess plaque burden will continue to be useful in the evaluation of promising atherosclerosis therapies.
Airway Smooth Muscle as a Target for Asthma Therapy
Julian Solway, M.D., and Charles G. Irvin, Ph.D.

The precise role of airway smooth muscle in the pathogenesis of asthma remains uncertain. The contraction of airway smooth muscle certainly causes acute narrowing of the airway and airflow obstruction in asthma, and smooth-muscle mass is increased in asthmatic airways. However, whether airway smooth muscle generates sufficient force in vivo to account for the excessive airway obstruction that characterizes asthma is unknown. Abnormalities in the dynamics of contraction, in the capacity of smooth muscle to maintain shortening in the face of load fluctuations imposed by tidal breathing, or in the capacity to relax represent other important mechanisms by which airway smooth muscle might contribute to airway narrowing in asthma. Beyond these mechanical effects, airway smooth muscle probably contributes to inflammation of the airway by secreting cytokines, modifying the tissue matrix, binding migratory inflammatory cells, or all three (Fig. 1). Whatever its role in asthma may be, it seems clear that airway smooth muscle could not contribute to asthma pathogenesis if it were absent.

In this issue of the Journal, Cox and colleagues report a clinical benefit of a novel approach to asthma therapy — bronchial thermoplasty. In this procedure, during three separate treatment visits, radiofrequency current is applied to the walls of the central airways through a bronchoscopically placed probe. Studies in animals and humans have shown that such treatment reduces the airway smooth-muscle mass but causes epithelial damage that resolves over time. In patients with moderately severe asthma, bronchial thermoplasty reduced airway responsiveness to an inhaled constrictor and modestly increased flow rates — effects that persisted for at least a year. The study by Cox and colleagues extends those findings by showing improvements in symptoms and quality of life and by reducing the use of rescue medication in subjects with moderate or severe asthma during periods when long-acting β₂-adrenergic agonists were withdrawn. That these effects occurred without significant increases in the forced expiratory volume in 1 second or a reduction in airway hyperresponsiveness suggests either that smooth-muscle-mediated airway constriction beyond the central airways accessible on bronchoscopy is clinically important or that mechanisms independent of airway smooth muscle, such as airway closure, contribute to airflow obstruction in subjects with asthma.

The mechanism underlying the effect of bronchial thermoplasty in asthma has not been fully established and might include changes other than the loss of airway muscle. For example, bronchial thermoplasty alters properties of airway epithelium, mucus glands, nerves, or

![Figure 1. Features of the Normal Airway and the Asthmatic Airway.](image-url)

In normal airways, smooth muscle might provide structural support, help regulate gas exchange, and contribute to mucus clearance, defense mechanisms, and cough, or it might be vestigial (resulting from lung development) and not play an important role. In asthma, airway smooth muscle mediates acute bronchoconstriction and participates in airway hyperresponsiveness. Accumulating evidence implicates smooth muscle in the pathogenesis of airway inflammation and remodeling and points to interactions with bronchial epithelium and nerves. The benefit of current asthma treatments, including bronchodilators, inhaled corticosteroids, and anti-IgE antibody, as well as bronchial thermoplasty, may be due in part to their actions on airway smooth muscle. Potential therapies (now theoretical) that target airway smooth-muscle contraction or abundance might include the induction of apoptosis of airway myocytes, alteration of transcription to shut down expression of the contractile apparatus, paralysis of airway smooth muscle, and enhancement of force-fluctuation-induced relengthening of airway smooth muscle.
blood vessels or modifies the character of airway inflammation in such a way that asthma-related symptoms are reduced as a result of either alterations in airway sensation or a genuine reduction in steady or episodic airway narrowing. What seems certain, however, is that bronchial thermoplasty reduces the smooth-muscle mass in the airway wall. This well-documented effect, together with the beneficial clinical effects suggested in the report by Cox and colleagues and in previous studies, highlights the potential usefulness of targeting airway smooth muscle in the treatment of asthma.

Indeed, a number of current treatments already exert some beneficial effects by acting on airway smooth muscle (Fig. 1). Inhaled β2-agonists often relax airway smooth muscle and can enhance the nuclear entry of glucocorticoids, thereby potentiating their antiinflammatory effect. Glucocorticoids inhibit the proliferation and migration of airway myocytes and suppress their expression of a number of proinflammatory cytokines. Anti-IgE antibody might also modulate the function of airway smooth muscle, since the low-affinity IgE receptor is expressed on airway smooth muscle and sensitization with IgE increases its force generation, impairs relaxation, and stimulates cytokine production. Furthermore, exposure to serum from persons with atopy increases the velocity of contraction of human bronchial rings; this increased velocity is thought to enhance the shortening of airway smooth muscle and to confer resistance to the relengthening of the muscle induced by force fluctuations. Perhaps anti-IgE antibody also prevents these phenomena.

Bronchial thermoplasty represents a novel approach to targeting airway smooth muscle, but it ablates airway myocytes only in bronchi 3 mm or larger in diameter, which can be treated directly. For this reason, and because of the considerable effort involved (three separate bronchoscopic procedures, each with a small but significant risk of complications), notable adverse effects (in the short term, at least), and likely expense, bronchial thermoplasty will probably need further refinement if it is to emerge as a widely applicable, practical treatment for moderate or severe asthma. Nonetheless, the results reported by Cox and colleagues suggest that we should now contemplate other approaches to targeting airway smooth muscle that might prove to be less invasive, more practical, and more amenable to application throughout the airways. Among the approaches envisioned is the possibility of ridding the airways of smooth muscle by stimulating apoptosis of airway myocytes. Alternatively, since many of the genes encoding smooth-muscle contractile-apparatus proteins require a common, relatively muscle-specific transcription factor (serum response factor) for transcriptional activation, it might be possible to antagonize the activity of the serum response factor and in that way shut down expression of the contractile apparatus. Depletion of contractile proteins should prevent smooth-muscle-mediated airway constriction and thus might prevent the occurrence of acute asthma attacks.

Another approach to preventing contraction might be to attack the integrity of contractile filaments (e.g., destroying actin filaments by activating coflin, an actin-binding protein that depolymerizes filamentous actin) or to block the linking of contractile myofilaments to focal adhesions at the cell surface, thereby preventing the transmission of the contractile force generated within each myocyte to the surrounding tissue. Finally, ways might be discovered to magnify the antiobstructive effect of tidal breathing, in which fluctuations in the tidal force transmitted through parenchyma–airway interactions relengthen shortened airway smooth muscle even during continued contractile stimulation. An airway that cannot remain constricted for long cannot cause prolonged airflow obstruction.

In medicine, pioneering approaches have often been replaced by other approaches with similar goals but better means of implementation. Vagotomy, for example, which was performed to reduce acid secretion in peptic ulcer disease, has been replaced by treatment with H₂-receptor antagonists and proton-pump inhibitors, which also reduce acid secretion. We expect that bronchial thermoplasty may be refined to become more effective and more practically applicable, but we also hope that the lessons it has already taught will prompt the development of other novel approaches that target the contribution of airway smooth muscle to the pathogenesis of asthma.
Dr. Solway reports receiving consulting fees from Merck, Tanox, AstraZeneca, and Critical Therapeutics and royalties from patents held by the University of Chicago and licensed to Boston Scientific. Dr. Irvin reports receiving consulting fees from Merck, Methapharm, and Genentech; lecture fees from Medical Graphics, Merck, Sepharoc, AstraZeneca, and Critical Therapeutics; and research grants from Sepharoc and GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

From the Department of Medicine, University of Chicago, Chicago (J.S.); and the Vermont Lung Center, Department of Medicine, University of Vermont, Burlington (C.G.I.).

Idiopathic Pulmonary Fibrosis — New Insights
Subodh Verma, M.D., Ph.D., and Arthur S. Slutsky, M.D.

“Death occurred about three months and a half after the onset of the acute disease and the lung was two thirds of the normal size, grayish in color, and hard as cartilage. Microscopically these areas showed advanced fibrotic changes and great thickening of the alveolar walls.” Thus did Sir William Osler describe, in 1892, a case of idiopathic pulmonary fibrosis — an unrelenting and progressive disease that afflicts more than 5 million patients worldwide. The number of patients who receive this diagnosis has doubled within the past decade, and yet there is no effective treatment. The overall prognosis is dismal, with a median survival of 3 to 5 years after diagnosis. Insights into the molecular mechanism of the disease, such as those provided by Armanios et al. in this issue of the *Journal* and Wang et al. in a recent report, are therefore especially valuable.

The disease is characterized by diffuse interstitial fibrosis with only mild inflammation, honeycomb cysts, and fibroblast foci; the intervening lung tissue is largely spared. Fibroblast foci are areas of fibroblasts and connective tissue and are located just beneath hyperplastic type 2 pneumocytes. Similar pathological features can be found with well-defined conditions such as collagen vascular diseases, Goodpasture’s syndrome, and asbestosis, so known causes must be ruled out before making the diagnosis of idiopathic pulmonary fibrosis.

As its name suggests, idiopathic pulmonary fibrosis is a disorder with an enigmatic pathogenesis. Although many investigators have underscored intraalveolar inflammation as a cause, antiinflammatory agents and immune modulators have proved to be minimally effective in limiting alveolitis and modifying the natural course of the disease.

It is currently believed that idiopathic pulmonary fibrosis is an epithelial–fibroblastic disease, in which unknown endogenous or environmental stimuli disrupt the homeostasis of alveolar epithelial cells, resulting in diffuse epithelial-cell activation and aberrant epithelial repair. Activated epithelial cells are thought to release potent fibrogenic molecules and cytokines, such as tumor necrosis factor α and transforming growth factor β1 (TGF-β1), which in turn foster the transformation of fibroblasts into myofibroblasts and promote their production of extracellular matrix molecules. TGF-β1 has been widely implicated in the development and progression of pulmonary fibrosis and, through an intricate signaling cascade, promotes the transcription of collagen type 1 and fibronectin in fibroblasts. A vicious cycle of injury and abnormal epithelial healing sets the stage for progressive fibrosis and architectural distortion of the lung parenchyma.

Wang et al. implicate caveolin-1 as a protective regulator of pulmonary fibrosis. Caveolin-1 limits TGF-β1–induced production of extracellular matrix and restores alveolar epithelial-repair processes. It is the predominant structural protein of caveolae, which are flask-shaped invaginations of the plasma membrane and are abundantly present in many terminally differentiated cells. These plasmalemmal microdomains serve many fundamental biologic processes, including vesicular and cholesterol trafficking and transcytosis. They represent a regulatory hub controlling the signaling activity of many molecules, including nitric oxide.

Wang et al. used several strategies to test the hypothesis that caveolin-1 is an endogenous inhibitor of pulmonary fibrosis. First, they observed that expression of the molecule was markedly reduced in lung tissue from patients with idiopathic pulmonary fibrosis and that this reduction was predominant in alveolar epithelial cells. Furthermore, they found that fibroblasts, the key cellular element of fibrosis, had low levels of caveolin-1 expression in patients with idiopathic pulmonary fibrosis. Second, intratracheal administration of caveolin-1 conferred resistance against bleomycin-induced fibrosis in mice and restored lung structural integrity.
Figure 1. Caveolin-1, the Telomere, and Pulmonary Fibrosis.

A recent study by Wang et al.\(^4\) shows that caveolin-1, the most abundant protein found within caveolae, inhibits TGF-\(\beta1\)–mediated production of extracellular matrix protein by fibroblasts and attenuates the development of pulmonary fibrosis in a mouse model of the disease. They also show that TGF-\(\beta1\) can mute this effect by repressing the expression of caveolin-1. TGF-\(\beta1\) has also been shown to negatively regulate telomerase activity. A study by Armanios et al.\(^3\) in this issue of the journal shows an association among mutant telomerase, short telomeres, and familial idiopathic pulmonary fibrosis.
The authors also observed an inverse relationship between caveolin-1 and TGF-β1 signaling. TGF-β1 attenuated the expression of caveolin-1 in human pulmonary fibroblasts, but overexpression of caveolin-1 suppressed TGF-β1-induced production of extracellular matrix protein by fibroblasts (Fig. 1). Thus, decreased caveolin-1 expression may unleash TGF-β1 signaling in epithelial cells and fibroblasts. TGF-β1 negatively regulates telomerase activity, the key regulator of telomere length, cell division, and senescence. Armanios et al. report that genetic mutations affecting telomerase may also increase susceptibility to idiopathic pulmonary fibrosis. Assessing caveolin-1 expression in patients with mutant telomerase may uncover a link between molecular signaling and a genetic predisposition to idiopathic pulmonary fibrosis.

The observations of Wang et al. show that caveolin-1 is a novel and essential regulator of fibroblast proliferation and suggest that it is a logical target for therapeutic intervention to reduce the development and progression of idiopathic pulmonary fibrosis. Treatment approaches that augment caveolin-1 bioavailability may help restore normal alveolar epithelial repair and regeneration and may help patients with idiopathic pulmonary fibrosis breathe more easily and live longer.

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

From the Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, and the University of Toronto — all in Toronto.


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Bevacizumab for Non–Small-Cell Lung Cancer

TO THE EDITOR: In their report on chemotherapy plus bevacizumab for non–small-cell lung cancer, as compared with chemotherapy alone, Sandler and colleagues (Dec. 14 issue) conclude that the addition of bevacizumab to paclitaxel and carboplatin has a significant survival benefit but is associated with an increased risk of treatment-related death. According to their results, 12 patients need to be treated to prevent one death at 1 year, at the price of an excess of one death from toxic effects for every 24 patients treated. Clearly, the balance between benefit and risk is questionable.

Marina Chiara Garassino, M.D.
Ospedale Fatebenefratelli e Oftalmico
20121 Milan, Italy
marina.garassino@fbf.milano.it

Valter Torri, M.D.
Istituto Mario Negri
20157 Milan, Italy


TO THE EDITOR: Sandler et al. show a survival benefit of bevacizumab in non–squamous-cell non–small-cell lung cancer, but pulmonary hemorrhage in their patients is a worrisome complication. Further clarification of the risk factors for this complication is needed. The phase 2 trial reported by Johnson et al.4 showed an association between hemoptysis and centrally located tumors and tumor cavitation; were these features present in the patients in the study reported by Sandler et al? Some patients with pulmonary hemorrhage had episodes of minor hemoptysis preceding the fatal event; how many other patients in the bevacizumab group had minor (grade 1 or 2) hemoptysis, and can minor hemoptysis truly be used as a warning sign?

Geoffrey R. Oxnard, M.D.
Massachusetts General Hospital
Boston, MA 02114

TO THE EDITOR: Before recommending, as Sandler and colleagues do, the routine use of bevacizumab combined with chemotherapy for non–squamous-cell, non–small-cell lung cancer, we should consider that cisplatin-based chemotherapy is superior, in terms of survival, to carboplatin-based chemotherapy when combined with a third-generation drug.1, 2 In addition, Rosell et al. showed that survival was better when paclitaxel was combined with cisplatin, rather than with carboplatin.3 The objective response rate in the control group


1373 Bevacizumab for Non–Small-Cell Lung Cancer
1375 Human H5N1 Influenza
1377 Fetal Pulse Oximetry and Cesarean Delivery
1378 Glycemic Durability of Monotherapy for Diabetes
1381 Teaching Surgical Skills
1381 A Medical Mystery: Dilated Bowel — The Answer
1382 Ovarian Transplantation in a Series of Monozygotic Twins Discordant for Ovarian Failure
in the study by Sandler and colleagues was surprisingly low (15%), in contrast to the rates that are usually reported (20 to 30%). This point suggests a potential selection bias.

Jean-Paul Sculier, M.D., Ph.D.
Anne-Pascale Meert, M.D.
Marianne Paesmans, M.Sc.
Institut Jules Bordet
1000 Brussels, Belgium
sculier@bordet.be


TO THE EDITOR: In the study by Sandler et al., the exclusion criteria were quite restrictive. Were patients who discontinued the use of aspirin, other antiplatelet drugs, nonsteroidal antiinflammatory agents, or anticoagulants included in the trial? “Clinically significant cardiovascular disease” and “medically uncontrolled hypertension” need to be defined clearly, since they are common conditions and were exclusion criteria. In addition, “predominantly” squamous-cell cancer needs to be defined. It would be useful for the practicing oncologist to know the number of patients who had poorly differentiated (not otherwise specified) non–small-cell lung cancer.

Guru Sonpavde, M.D.
U.S. Oncology Research
Houston, TX 77598
guru.sonpavde@usoncology.com

THE AUTHORS REPLY: Garassino et al. express concern regarding the balance between risk and benefit with the addition of bevacizumab. Despite a modest increase in treatment-related deaths, the addition of bevacizumab to chemotherapy yielded an absolute improvement in survival of nearly 7% at 1 and 2 years. These data prompted the Food and Drug Administration to approve bevacizumab for the treatment of non–squamous-cell lung cancer.

In reply to Oxnard, episodes of minor hemoptysis were not routinely captured on the case-report forms. To assess for possible risk factors for hemoptysis, we conducted a retrospective case–control study that included patients from both our phase 2 and phase 3 studies.1 In this analysis, baseline hemoptysis and tumor cavitation were noted as risk factors. However, the interpretation of these data is limited by the low incidence of clinically significant pulmonary hemorrhagic events.

We agree that cisplatin may be slightly superior to carboplatin on the basis of recent meta-analyses; however, we observed no survival advantage with cisplatin, as compared with carboplatin, in our randomized trial (E1594), which predated the cited meta-analyses.2 The results of the E1594 trial, coupled with the results of the pilot phase 2 trial,3 led to the selection of carboplatin-based therapy for the phase 3 trial (E4599). In any case, the E4599 trial clearly isolates the additional survival benefit with bevacizumab plus the carboplatin-based regimen. A recently completed European trial of cisplatin and gemcitabine with or without bevacizumab will help address the concern of Sculier et al.

Sonpavde questions the eligibility criteria used in our study. To clarify, patients could not receive any antiplatelet agent (other than aspirin at a dose of less than 325 mg daily) or anticoagulant. The protocol did not specify a washout period for antiplatelet agents; however, in practice, delaying the start of bevacizumab until after the antiplatelet effect has dissipated is reasonable. In the protocol, we defined clinically significant cardiovascular disease as “symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.” On enrollment, blood pressure had to be less than or equal to 150/100 mm Hg while patients were receiving a stable regimen of antihypertensive drugs.

With regard to histologic features, we used the following eligibility criterion in the protocol: “Patients must have histologically or cytologically confirmed non–small-cell lung cancer except squamous-cell carcinoma. Mixed tumors will be categorized by the predominant cell type.” Of our
850 patients, 585 had adenocarcinoma, and 46 had large-cell carcinoma.
Alan Sandler, M.D.
Vanderbilt University
Nashville, TN 37235
alan.sandler@vanderbilt.edu

Robert Gray, Ph.D.
Dana–Farber Cancer Institute
Boston, MA 02115

David H. Johnson, M.D.
Vanderbilt University
Nashville, TN 37235


TO THE EDITOR: As is consistent with previous studies of outbreaks of avian influenza A (H5N1) virus, the epidemiologic investigations reported by Kandun et al. in Indonesia and by Oner et al. in Turkey (Nov. 23 issue) show that H5N1 virus primarily infects young people (median age, 9 years). As of late November 2006, 258 cases of human H5N1 virus infection had been identified. More than half of the patients were under the age of 20 years (median age, 18.5 years), and 25% of them were under the age of 10 years. Although both studies report clusters within families and cite exposure to dead poultry as a common risk factor, it is unlikely that the intensity of exposure differed among household members. Rather, higher incidence rates in children may represent age-dependent differences in host susceptibility to H5N1 virus infection. Human infection is mediated by a receptor recognized by avian influenza (α2,3-linked sialic acid) that is expressed in the lower respiratory tract. In children this receptor may be expressed in the upper airway, increasing the risk of infection. Indeed, α2,3-linked sialic acids are homogeneously distributed in the human fetal lung, and the expression of the receptor appears to decrease with age.

Miguel Goicoechea, M.D.
University of California, San Diego
San Diego, CA 92103
mgoicoechea@ucsd.edu


Human H5N1 Influenza

TO THE EDITOR: Human H5N1 virus infection can be difficult to diagnose. In the report by Oner et al., the results of nasopharyngeal swabs were mostly negative. Positive results were obtained on polymerase-chain-reaction (PCR) assays of tracheal aspirates and lung-tissue samples. These results are predictable, since the receptors for the attachment of H5N1 virus are located predominantly around alveoli and terminal bronchioles and become progressively more rare toward the trachea.

Jeanne A. Pawitan, M.D., Ph.D.
University of Indonesia
Jakarta 10430, Indonesia
jeanneadiwip@yahoo.com


TO THE EDITOR: The Perspective article by Webster and Govorkova accompanying the reports by Kandun et al. and Oner et al. is perhaps the best available published summary of the emergence, evolution, and proliferation of H5N1 virus, an important emerging animal and human pathogen. Nonetheless, the time line that the authors provide does not include the four retrospectively confirmed cases of human H5N1 virus infection that occurred in Korea between December 2003 and March 2004 and another five confirmed cases that occurred in Japan during February and March 2004 among poultry workers and persons involved in the culling of infected poultry. The cases in

Japan were not reported until 10 months after they had been confirmed, and the cases in Korea were not confirmed until more than 2 years after they had occurred. The existence of these often overlooked nonfatal cases of human H5N1 virus infection illustrate the many impediments we face in refining our understanding of the epidemiology, risks, and potential effects of this disease in human populations.

Joseph P. Dudley, Ph.D.
Science Applications International
Arlington, VA 22203
dudleyjp@saic.com


Dr. Oner and colleagues reply:
That the expression of α2,3-linked sialic acid receptor might be a reason for the high incidence of the disease in young patients is theoretical. To assess this concern, an understanding of the culture and traditions of the countries where avian influenza outbreaks have occurred is required. In the families of the patients in our study, exposure was more intensive in children than in their parents. People in this area of Turkey do not believe that the illness of chickens can be transmitted to humans. Therefore, the children played with the poultry, kissing and sleeping with them even when the birds were ill. However, the parents typically had contact with the chickens only while preparing them for cooking and eating them. We believe that contact with the secretions of the sick birds is an important risk factor and that children had more intensive contact with the poultry. Furthermore, if there were a relationship between viral-receptor intensity in young children and disease incidence, we would expect to see more cases in the first years of life, which has not been observed. Cerna et al. have studied sialic acid expression in relation to developmental maturity of the lung and have shown that there is a slight decrease in sialic acid expression in the lungs before birth. Therefore, we think that children are affected by avian influenza viruses by the same mechanism that mediates adult infection.

We agree with Pawitan that human H5N1 virus infection is difficult to diagnose. Although the results of some nasopharyngeal swabs were negative in our study, all tracheal aspirates and lung-tissue samples were positive on real-time PCR assay. As Pawitan states, the receptors for the attachment of avian influenza virus are located mostly around alveoli and terminal bronchioles.

Ahmet Faik Oner, M.D.
Yuzuncu Yil University
65200 Van, Turkey
af659@yahoo.com

Mehmet Ceyhan, M.D.
Hacettepe University
06100 Ankara, Turkey

Hayrettin Akdeniz, M.D.
Yuzuncu Yil University
65200 Van, Turkey


Dr. Kandun and colleagues reply:
Most human cases of highly pathogenic H5N1 virus infection have been sporadic to date, but family clusters have occurred in several countries. Direct physical contact with sick or dead poultry has been identified as the primary risk factor. The reported intensity of exposure to diseased or dead poultry can vary substantially among family members in households of patients who have H5N1 virus infection. In our study, all three patients and the unaffected family members in cluster 3 were similarly exposed to diseased or dead poultry, as were many neighbors who never became ill. No patients or unaffected family members in clusters 1 and 2 had known contact with sick or dead poultry. In addition to exposure to H5N1 virus, susceptibility to human infection with H5N1 viruses could be mediated by age or immunologic, genetic, or other factors. The question of whether genetic or other factors, such as those affecting the expression of the host inflammatory response, might influence the severity of disease after H5N1 virus infection should also be investigated.

In our study, throat specimens had a higher yield for detecting H5N1 virus than did nasal specimens, and H5N1 viral RNA levels were higher in throat specimens than in nasal specimens in another study. For detection of H5N1 viral RNA by real-time PCR in patients with suspected H5N1 virus infection, specimens should be collected from different respiratory sites on multiple days, including nasal and throat swabs from patients who are not undergoing mechanical ventilation and endotracheal aspirates from intubated pa-
Testing of nasal-swab specimens from patients with suspected H5N1 virus infection can also help detect human influenza A and B viruses that bind to α2,6-linked sialic acid receptors located primarily in the upper respiratory tract. Two minor inaccuracies appear on page 2188 of our article. In Figure 1, the hospitalization date for Patient 2A should have been 9/6, rather than 9/3. On the same page, under the heading “Cluster 2,” line 3 of the second paragraph should have read, “Four days after his aunt was hospitalized, he had onset of fever,” rather than “three days.” We regret the errors.

I. Nyoman Kandun, M.D., M.P.H.
Ministry of Health
Jakarta 10560, Indonesia

Endang R. Sedyaningsih, M.D., D.P.H.
National Institute of Health Research and Development
Jakarta 10560, Indonesia

Timothy M. Uyeki, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA 30333
tuyeki@cdc.gov


Fetal Pulse Oximetry and Cesarean Delivery

TO THE EDITOR: The study of fetal pulse oximetry and cesarean delivery reported by Bloom et al. (Nov. 23 issue)1 perhaps gives us an interesting insight into clinicians’ behavior. The authors claim that fetal oxygen monitoring does not alter the rate of cesarean delivery. However, the reason for the lack of differences in cesarean rates and infant outcomes between the “masked” and “open” groups may reflect the difficulty of the clinicians in interpreting the fetal oxygen saturation values and therefore in including this information in intrapartum management. In support of this suggestion, among the patients with reassuring fetal heart-rate tracings, 25.1% had low oxygen saturation. If the clinicians had been acting on their knowledge of the oxygen saturation levels, one would expect a higher rate of cesarean section in the open group than was reported. The fact that intrapartum management was left to the discretion of the attending physician, without any clear guidelines on abnormalities in the level of fetal oxygen saturation and in the duration and frequency of low values, makes uncertain the authors’ conclusion that the knowledge of fetal oxygen saturation may be of no benefit.

Michael J. Peek, Ph.D.
George S. Condous, M.B., B.S.
Ralph K.H. Nanan, Ph.D.
University of Sydney
Penrith 2750, Australia
peekm@wahs.nsw.gov.au


THE AUTHORS REPLY: We differ with the assertion by Dr. Peek and colleagues that we failed to provide attending physicians with clear guidelines regarding an abnormal level of fetal oxygen satu-

TO THE EDITOR: The study of fetal pulse oximetry and cesarean delivery reported by Bloom et al. (Nov. 23 issue)1 perhaps gives us an interesting insight into clinicians’ behavior. The authors claim that fetal oxygen monitoring does not alter the rate of cesarean delivery. However, the reason for the lack of differences in cesarean rates and infant outcomes between the “masked” and “open” groups may reflect the difficulty of the clinicians in interpreting the fetal oxygen saturation values and therefore in including this information in intrapartum management. In support of this suggestion, among the patients with reassuring fetal heart-rate tracings, 25.1% had low oxygen saturation. If the clinicians had been acting on their knowledge of the oxygen saturation levels, one would expect a higher rate of cesarean section in the open group than was reported. The fact that intrapartum management was left to the discretion of the attending physician, without any clear guidelines on abnormalities in the level of fetal oxygen saturation and in the duration and frequency of low values, makes uncertain the authors’ conclusion that the knowledge of fetal oxygen saturation may be of no benefit.

Michael J. Peek, Ph.D.
George S. Condous, M.B., B.S.
Ralph K.H. Nanan, Ph.D.
University of Sydney
Penrith 2750, Australia
peekm@wahs.nsw.gov.au


THE AUTHORS REPLY: We differ with the assertion by Dr. Peek and colleagues that we failed to provide attending physicians with clear guidelines regarding an abnormal level of fetal oxygen satu-
ration. Indeed, we believe that a major strength of our study was the effort taken to ensure the proper education of our health care providers. These efforts, as summarized in the Methods section of the article, included three stages. First, specialized educators from the manufacturer participated in centralized training sessions, as well as individualized training sessions conducted at each of the 14 sites. These sessions included instruction on the interpretation of values for fetal oxygen saturation. Second, all attending physicians were required to pass examinations, which included questions regarding such interpretation, before they could participate in the trial. Third, a mandated refresher course was conducted after the second year of the trial. It is our belief that such efforts ensured that participating physicians had a clear understanding of how to interpret levels of fetal oxygen saturation and that our conclusions remain valid.

Regarding the concern that the rate of cesarean delivery should have been higher in the open group than it was, it is important to remember that values of fetal oxygen saturation are supposed to be interpreted in the context of a non-reassuring fetal heart rate. That is, one would not expect the group of women with a reassuring fetal heart rate to have had an increased rate of cesarean section.

Steven L. Bloom, M.D.
University of Texas Southwestern Medical Center
Dallas, TX 75390
steven.bloom@utsouthwestern.edu

Catherine Y. Spong, M.D.
National Institute of Child Health and Human Development
Bethesda, MD 20892

Elizabeth A. Thom, Ph.D.
George Washington University Biostatistics Center
Rockville, MD 20852
for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network

Glycemic Durability of Monotherapy for Diabetes

TO THE EDITOR: Kahn et al. (Dec. 7 issue) report on A Diabetes Outcome Progression Trial (ADOPT), which assessed the glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. It is difficult to maintain target levels of glycated hemoglobin with the use of traditional oral antidiabetic drugs, owing to declining β-cell function. In ADOPT, the annual increase in glycated hemoglobin levels over a 4-year period in patients with newly diagnosed diabetes was greatest with glyburide, intermediate with metformin, and least with rosiglitazone. Our longitudinal data (for 2005–2006) from a nationwide general-practitioner database in Germany (Disease Analyzer) indicate similar findings. Among 12,304 patients with diabetes who were using oral antidiabetic drugs, the mean of the individual relative differences in glycated hemoglobin levels (those in 2006 divided by those in 2005) was 1.018 (95% confidence interval, 1.016 to 1.020). The mean relative difference in glycated hemoglobin levels was highest for glinides, followed by sulfonylureas, acarbose, metformin, and glitazones (Table 1). In multivariate logistic-regression analyses, the use of glitazones was associated with a significantly smaller increase in glycated hemoglobin levels than was the use of sulfonylureas, after adjustment for age, sex, the other oral antidiabetic drugs, health care use, and practice characteristics (P = 0.007); the same trend was observed for metformin (P = 0.048). Though all the oral antidiabetes drugs we studied are associated with progression of glycemia, our primary care data indicate the potential value of

Table 1. Baseline Glycated Hemoglobin Levels and Annual Change among Patients with Diabetes Who Were Treated with Oral Agents in Primary Care Practices.*

<table>
<thead>
<tr>
<th>Oral Agents</th>
<th>No. of Patients</th>
<th>Glycated Hemoglobin Level</th>
<th>P Value†</th>
<th>Mean Relative Difference in 2006 (95% CI):‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glitazones</td>
<td>1029</td>
<td>7.12±1.06</td>
<td>0.007</td>
<td>1.010 (1.002–1.017)</td>
</tr>
<tr>
<td>Metformin</td>
<td>8579</td>
<td>6.98±1.04</td>
<td>&lt;0.001</td>
<td>1.017 (1.015–1.019)</td>
</tr>
<tr>
<td>Acarbose</td>
<td>873</td>
<td>6.93±1.07</td>
<td>&lt;0.001</td>
<td>1.017 (1.010–1.024)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>5789</td>
<td>7.11±1.11</td>
<td>&lt;0.001</td>
<td>1.021 (1.017–1.024)</td>
</tr>
<tr>
<td>Glinides</td>
<td>894</td>
<td>7.08±1.10</td>
<td>&lt;0.001</td>
<td>1.025 (1.017–1.032)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. CI denotes confidence interval.
† P values, calculated with the use of paired t-tests, are for the difference between glycated hemoglobin levels in 2006 and those in 2005.
‡ The relative difference in glycated hemoglobin levels was calculated for each patient as the levels in 2006 divided by the levels in 2005.
and need for new agents in the treatment of diabetes.\(^2\)

Wolfgang Rathmann, M.D., M.S.P.H.
German Diabetes Center
40225 Düsseldorf, Germany
rathmann@ddz.uni-duesseldorf.de

Karel Kostev, M.A.
IMS Health
60528 Frankfurt, Germany

Burkhard Haastert, Ph.D.
German Diabetes Center
40225 Düsseldorf, Germany

Mr. Kostev reports being an employee of IMS Health, a consulting company that received a grant from Eli Lilly, Germany, to carry out a database study of longitudinal changes in glycated hemoglobin values in patients with diabetes in primary care. Drs. Rathmann and Haastert report receiving consulting fees from IMS Health for this study.


**TO THE EDITOR:** The conclusion by Kahn et al. that rosiglitazone slows the loss of β-cell function seems unwarranted. The three treatment groups started with similar baseline values for β-cell function, determined with the use of homeostasis model assessment (HOMA 2), and at the end of the study there was no significant difference in the values between the rosiglitazone group and the glyburide group and only a small difference between the rosiglitazone group and the metformin group. The rate of decline in β-cell function was greatest in the glyburide group because of an initial increase in β-cell function according to HOMA 2; it does not represent the true state of β-cell function. The stopping of all drugs or switching of all patients to a similar regimen for 3 months might have made clearer assessment possible.

Rajesh Garg, M.D.
Brigham and Women’s Hospital
Boston, MA 02115
rgarg@partners.org

Dr. Garg reports receiving speaking fees from Merck and Novartis.

**TO THE EDITOR:** ADOPT focused on the effect of diabetes medications on an end point of questionable importance to patients (the need for a second medication). In fact, ADOPT results leave patients in the dark as to whether they are better
off in important ways (the quality of life and risks of illness and death) with any of these agents, particularly given the burden of their adverse effects as reported for this trial.

ADOPT is not a special case: only 20% of randomized studies of diabetes have reported important patient outcomes. We believe the time has come for a broad consensus on a standard set of important outcomes for patients in diabetes trials, like the Outcome Measures in Rheumatology (OMERACT) initiative, in order to improve the relevance of such evidence for clinical decision making.

Ganjan Y. Gandhi, M.D.
Victor M. Montori, M.D.
Mayo Clinic College of Medicine
Rochester, MN 55905


THE AUTHORS REPLY: Gandhi and Montori discuss the need for clinical trials to examine outcomes such as morbidity and mortality. We agree, but this was not the aim of our study. Our study was designed to determine whether the loss of glucose control in patients with type 2 diabetes could be slowed, and we were able to answer this important question definitively. Since improved glucose control clearly reduces microvascular complications, slowing the progression of hyperglycemia would be expected to reduce morbidity and increase the quality of patients’ lives.

Parashar and Varma correctly mention that antihypertensive agents have dissimilar effects on glucose metabolism. Table 2 of our article shows the percentages of subjects with concomitant use of various antihypertensive agents at some time during the study. There was no significant difference in the use of these medications among the three groups; thus, differential use cannot explain the differences in glycemia that we observed. Similarly, concomitant use of aspirin ranged from 31.6% of patients in the glyburide group to 33.0% in the metformin group and therefore also cannot explain the differences in outcomes.

The importance of the rate of loss of β-cell function in determining the progression of type 2 diabetes is well documented. Garg is correct that β-cell function according to HOMA 2 was similar in the rosiglitazone group and the glyburide group at baseline and after 4 years of treatment. However, since the two medications have different mechanisms of action and establishment of their maximal biologic effectiveness takes months, we prespecified that our analysis would commence at 6 months. From then on, the rate of change differed markedly between the two groups, which partly explains the greater durability of the lowering of glucose levels with rosiglitazone. Since insulin sensitivity is a critical determinant of β-cell secretory demand, the similar β-cell function according to HOMA 2 among patients receiving rosiglitazone and those receiving glyburide, with better insulin sensitivity among patients receiving rosiglitazone, indicates that at the end of the study, the β cells of the patients receiving rosiglitazone were performing qualitatively better. With regard to the use of glucose-lowering medications before the study commenced, since no patients were taking these medications at the time of randomization, there was no need to discontinue their use or to use the same agent initially before switching to one of the three study treatments.

The primary care data reported by Rathmann et al. confirm our finding that glucose-lowering agents have differential effects in slowing the rate of progression of glycemia, providing support for our conclusion that the choice of initial monotherapy has to be guided by clinical efficacy along with a consideration of adverse events and costs. The challenge now is to develop new agents and approaches that can slow progression even more effectively.

Steven E. Kahn, M.B., Ch.B.
Veterans Affairs Puget Sound Health Care System
Seattle, WA 98108
skahn@u.washington.edu

Giancarlo Viberti, M.D., F.R.C.P.
King’s College London School of Medicine
London SE1 9RT, United Kingdom

for the ADOPT Steering Committee

Teaching Surgical Skills

TO THE EDITOR: Reznick and MacRae (Dec. 21 issue) report on the current status of simulation in surgical-skills training and its various applications. Another potential use of simulation is as a part of the curriculum for medical students, with an aim to introduce hands-on skills training and evaluation early in their career. During surgical clerkships, only 67% of surveyed students thought that the surgical teaching and exposure they had received was adequate, and the majority of the exposure involved minor, “less risky” parts of surgical procedures, such as tying knots or cutting sutures. Perhaps the exposure of students to surgical simulation would allow them to appreciate their own technical ability, would reveal whether they were interested in participating in technical procedures, and would therefore influence their choice of residency training.

Vani Dandolu, M.D.
Jordan Newmark, M.D.
Temple University Hospital
Philadelphia, PA 19140


THE AUTHORS REPLY: Drs. Dandolu and Newmark outline another potential application of training using surgical simulation. Although our article concentrated primarily on postgraduate training, we wholeheartedly agree that undergraduate students also benefit from training in a surgical-skills laboratory setting. In our institution, a trial program of skills training was implemented at one of the four major teaching academies. Other students demanded to be included, and we now offer laboratory-based skills training to every medical student at the beginning of the surgical clerkship. This type of training benefits not only future surgical residents but also all future physicians who require technical skills in their practice.

We would like to address one other issue relating to our article. Since its publication, we have heard from several colleagues who have correctly pointed out that William Stewart Halsted, the great American surgeon, was never knighted.

Helen MacRae, M.D.
Richard Reznick, M.D.
University of Toronto
Toronto, ON M5G 1L5, Canada
richard.reznick@utoronto.ca

A Medical Mystery: Dilated Bowel — The Answer

The medical mystery in the February 1 issue involved a 70-year-old man who presented with a history of increasing abdominal distention. The patient was evaluated by means of computed tomography (CT) after an abdominal radiograph raised concern about a sigmoid volvulus. The diagnosis of a colonic pseudo-obstruction was made after the CT scan and a follow-up contrast enema study showed dilated loops of colon extending to the rectum, without evidence of blockage or perforation. An underlying parasitic infection was ruled out by means of additional laboratory testing.

The CT scout image, however, provided a clue to the patient’s disease. With the patient lying still on a CT-scanner table, the scout image was acquired on a 64-detector–row CT scanner. The scout image was used to preview the area of interest for subsequent CT imaging. It revealed an unusual sinusoidal artifact involving the patient’s right forearm (Fig. 1A). The patient’s concurrent electrocardiogram (Fig. 1B) showed an analogous artifact, mimicking an atrioventricular block. This rhythm is in fact a normal sinus rhythm with superimposed, sharp pseudo-flutter waves (Fig. 1B) that are not associated with the QRS complex.

This case shows several features of a Parkinsonian tremor, while highlighting the association between Parkinson’s disease and a colonic pseudo-obstruction. The tremor is present at rest and is often confined to one limb. Besides the classic “pill-rolling” tremor, pronation-supination of the hand and forearm, as seen in this patient, is a common presentation. The frequency of the tremor is typically between 3 and 5 cycles per second. In this case, on the basis of a CT scout table velocity of 79 mm per second and an electrocardiographic sweep speed of 25 mm per second, the tremor frequency was esti-
mated to be 3 and 4 Hz by means of CT and electrocardiography, respectively — findings ultimately confirmed by direct visual observation.

Jason Handwerker, M.D.
Vassilios D. Raptopoulos, M.D.
Beth Israel Deaconess Medical Center
Boston, MA 02215
jhandwer@bidmc.harvard.edu


Editor’s note: We received 1475 responses to this medical mystery — 53% from physicians in practice, 26% from physicians in training, 16% from medical students, and 5% from other readers. Responses were received from 82 countries. Many of the responses reflect pathophysiological thinking as well as a team effort — such as the results of a discussion of the case during a teaching conference.

Ten percent of the respondents correctly diagnosed Parkinson’s disease, with tremor-induced changes in the right arm (on the scout film) and on the electrocardiogram, and the dilated bowel. Thirty-four percent diagnosed Chagas’ disease, which was probably due to the dilated bowel and presumed cardiac dysfunction. Twenty-one percent of the responses suggested a toxic metabolic cause, such as hypokalemia, hypomagnesemia, or adverse effects of medication (e.g., from digitalis or calcium-channel blockers); 11% suggested atrial fibrillation with mesenteric ischemia due to an embolic event; 5% diagnosed Ogilvie’s syndrome; and the remaining 19% diagnosed a variety of other conditions, such as toxic megacolon, amyloidosis, and Hirschsprung’s disease.

Ovarian Transplantation in a Series of Monozygotic Twins Discordant for Ovarian Failure

TO THE EDITOR: We previously reported in the Journal a case of a successful ovarian transplantation between 25-year-old monozygotic twins. One had undergone menopause at the age of 14 years, whereas the other was still fertile.1 After receiving a graft of ovarian tissue from her sibling, the previously menopausal twin conceived spontaneously during the second menstrual cycle and delivered a healthy full-term baby. Subsequently, 10 other pairs of monozygotic twins who were discordant for ovarian failure sought consultation at our center for ovarian transplantation. Four women
had previously failed to conceive after receiving donor eggs through in vitro fertilization (IVF), two also required surgery for fibroids or cysts, and all preferred the possibility of natural conception, the option to cryopreserve spare tissue for future use, and the advantage of undergoing a single procedure. We report on the outcomes of the seven twins who have already undergone ovarian transplantation.

All recipients had high follicle-stimulating hormone (FSH) levels and had had amenorrhea for 2 to 26 years (Table 1). In all cases of transplantation, ovarian graft tissue was obtained by unilateral oophorectomy, trimmed to approximately the same dimensions as the resected surface of the recipient ovarian medulla, and shaved to a thickness of approximately 1 mm to facilitate early revascularization. The medullary bed was sutured to the undersurface of the cortical graft with 9-0 sutures to maintain tight tissue approximation. All seven recipients resumed menses (range, 65 to 93 days after surgery), and by day 140 after transplantation, all had regular cycling, with a normal serum FSH level on day 3 of the menstrual cycle. There have been five pregnancies thus far (four were spontaneous and one was achieved through natural-cycle IVF), and the other women continue to have regular menstrual cycles, although after 2 years the FSH levels began to rise.

Genetically discordant premature ovarian failure in monozygotic twins is not as rare as we had previously assumed.\(^2\) Ten of the 11 cases that we have seen were apparently the result of congenital germ-cell deficiency, since histologic analysis verified the absence of primordial follicles and

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<th>Recipient No.</th>
<th>Age at Menopause (yr)</th>
<th>Pretransplantation FSH Level (mIU/ml)</th>
<th>Age at Transplantation (yr)</th>
<th>Time to First Menses (days)</th>
<th>Post-Transplantation FSH Level on Day 3 of Menses (mIU/ml)</th>
<th>Intermenstrual Interval (days)</th>
<th>Detection of Pregnancy</th>
<th>No. of Days after Transplantation</th>
<th>Cycle No.</th>
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* The intermenstrual interval is shown for all cycles after transplantation until pregnancy or until the time of reporting.
† This recipient has no ovaries or fallopian tubes; she will require in vitro fertilization.
there were no other antecedent diseases or exposures associated with ovarian failure.\(^3\) Identical twins, like animal clones, are not actually identical, owing to epigenetic variations such as DNA methylation. Recipient 7 had had acute lymphoblastic leukemia more than 4 years before ovarian transplantation and had also received a bone marrow transplant (which is what caused her ovarian failure) from her sister, who has not had cancer. Unlike her sister, she also had a large nevus on her face. Recipient 5 had type 1 diabetes, whereas her twin had normal glucose levels but had a history of Graves’ disease. These are all diseases for which there is a recognized genetic predisposition\(^4\) and that were discordant in these monozygotic sisters.

The type of twinning was known for six of the pairs of monozygotic twins. Three of the six were monochorionic and monoamniotic (incidence, 50%), which is normally rare among twin pregnancies (incidence, 1 to 3%; \(P<0.005\)).\(^5\) This suggests that late splitting of embryos may be associated with discordant ovarian function, which could be due to either misallocation of early germ-cell precursors or increased epigenetic instability of genes regulating oogenesis.\(^6\)

Our transplantation results should encourage continued efforts to bank ovarian tissue for patients with cancer, in anticipation of reimplantation after remission. More speculatively, these procedures could enable healthy women to extend their reproductive life span.

Sherman J. Silber, M.D.
St. Luke’s Hospital
St. Louis, MO 63107
silber@infertile.com

Roger G. Gosden, Ph.D., D.Sc.
Weill Medical College of Cornell University
New York, NY 10021


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More than four decades ago, Don O’Donoghue wrote the first comprehensive book on sports medicine (Treatment of Injuries to Athletes. Philadelphia: Saunders, 1962) — a subspecialty that did not even formally exist at the time. The book addressed the issues that would be faced by the team physician at a high school or college, and it included descriptions of many of the surgical procedures performed on athletes.

All of us in sports medicine would like to think that high school, college, or professional athletes are the focus of our specialty. In reality, however, most sports medicine practices treat recreational athletes. And although they are generally older and less well conditioned than professionals, present with problems later, and often lack the resources — including time — to devote to treatment and rehabilitation, these patients expect care that is the same as that given to high-level athletes.

Clinical Sports Medicine addresses the care of both recreational and professional athletes. It contains 72 chapters written by 132 contributors, some of whom are venerable in the field of sports medicine, and it describes nearly every medical or surgical condition that might be encountered in sports medicine. Topics are organized by anatomical system, and each chapter includes a comprehensive description of the means of establishing diagnoses, as well as a decision tree for choosing treatments. For cases in which surgery is a prominent part of management, the procedures are often described.

Some surgical procedures are performed much more frequently in professional athletes than in recreational athletes, but the procedures the two groups receive differ little. What is different in the treatment received is the rehabilitation, because the professional athlete must return to a higher level of activity and performance than the recreational athlete. Rehabilitation is thus the essence of sports medicine practice. Recognizing this, the editors of this book have devoted five comprehensive, anatomically oriented chapters to the principles of rehabilitation. In addition, specific rehabilitation programs for nearly every condition are described.

Particularly comprehensive — and readable — are the chapters on muscle injuries, on the female athlete, and on the principles of rehabilitation. Chapter 10, entitled “The Mature Adult Athlete,” on the other hand, is little more than a description of the sports limitations following joint replacements — giving short shrift to an ever-enlarging segment of sports medicine practice. Likewise, chapter 7, “The Psychological Aspects of Healing the Injured Athlete,” does not do justice to this burgeoning topic.

Although the book leans heavily toward the surgical management of sports injuries — as one would expect in a volume written principally by orthopedic surgeons — it nonetheless does justice to the diagnosis and management of nonsurgical conditions. It stands out as the most up-to-date and comprehensive book dealing with clinical sports medicine.

James G. Garrick, M.D.
St. Francis Memorial Hospital
San Francisco, CA 94109
Interventions Following Mass Violence and Disasters: Strategies for Mental Health Practice


The response to a major disaster is beset by logistical problems, not least of which is that the means of implementing interventions that are meant to aid the victims are also disrupted. One of the strengths of Interventions Following Mass Violence and Disasters is that it places the response to concerns about mental health within the fragmented environment that follows a catastrophe. Although the book contains useful advice on practical mental health interventions, its real goal is to outline what we know and what we do not know about this kind of intervention. Chapter 5 provides an excellent discussion of how to monitor and evaluate the mental health services offered in the aftermath of disaster, stressing the importance of getting “buy-in” on the plan of action from all parties involved throughout the course of the intervention.

The authors of each chapter provide clear summaries of the literature about mental health interventions in the wake of terrorism, tsunamis, and other catastrophes, tending to focus on research related to post-traumatic stress disorder. The section on preparation and assessment contains several excellent papers on resilience and assessment of needs. The chapters in the middle section of the book neatly divide strategies into immediate, early, intermediate, and long-term interventions. They review the literature on each, providing practical recommendations and acknowledging the limitations of each strategy.

The last two chapters of the book discuss future directions. Authors Litz and Gibson examine the ethical imperatives for studying and learning from postdisaster initiatives in a concerted way. They assert that “it is arguably the failure to conduct RCTs [randomized, controlled trials], rather than to implement them, that represents an ethical problem.” A case in point is psychological debriefing and clinical incident debriefing, which are well-studied postcrisis interventions. Several of the book’s contributors note that these techniques have been shown to lack efficacy and that they “may be associated with more adverse outcomes.”

Ursano and Friedman, in the final chapter of the book, point out what is at stake: “the disaster community is often flooded with outsiders” who can not only disrupt the community further but also consume valuable local resources. Given that most people and communities appear to recover after a disaster, the outsiders and the professionals who offer services are obliged to make sure that they are really needed. This book reminds us that ignorance and good intentions are no excuse for doing harm.

There are many lingering questions. To what extent do acute stress disorder and post-traumatic stress disorder account for the psychological suffering in the wake of a disaster? And by collecting symptoms under the rubric of specific disorders, however reliable and valid the rubric may be, are we not also making the assumption that treatment can be generalized? This is a field full of questions that need to be answered not only very carefully but also in great depth.

Schuyler W. Henderson, M.D.
Columbia University
New York, NY 10030
henderss@childpsych.columbia.edu

Andrés Martin, M.D., M.P.H.
Yale Child Study Center
New Haven, CT 06520

Bioethics and Armed Conflict: Moral Dilemmas of Medicine and War


The graphic photographs released in 2003 depicting prisoner abuse at Abu Ghraib evoked a swift and strong worldwide response of shock, dismay, and condemnation and led to multiple investigations, revision of detention and interrogation procedures, and punishment of military personnel. More recent reports, in this journal and elsewhere, of U.S. military physicians’ involvement in the torture of prisoners in Iraq, Afghanistan, and Cuba raise critical and complex questions about the appropriate scope of the activities of military physicians. As the first single-author, book-length examination of the roles and responsibilities of physicians in war, Michael
Gross’s *Bioethics and Armed Conflict* is a timely addition to the growing literature on military medical ethics.

Early in the book, Gross offers a description and comparison of fundamental moral principles in medicine and in war. He then uses these principles to analyze a variety of moral questions confronted by military physicians. For example, who should receive medical treatment in war? What health care rights should military personnel enjoy? Should military physicians be impartial in treating the wounded? Should medical personnel and facilities be granted immunity from attack? Should military physicians participate in torture as a means of gaining vital information? Should physicians assist in the development of new chemical and biologic weapons?

Physicians reading *Bioethics and Armed Conflict* are likely to find the author’s answers to these questions highly provocative. Gross considers and almost completely rejects the standard guidelines for physicians in war that are contained in the Geneva Conventions and in policy statements of professional organizations such as the World Medical Association. The view articulated in those documents is that of the military physician as impartial and above the fray, basing decisions about medical treatment solely on medical criteria of need, strictly refraining from any complicity in torture or in the development of chemical or biologic weapons, and relying on the same bioethical principles to guide professional practice in wartime and in peacetime.

In sharp contrast to this traditional view, Gross argues that the demands of war require military physicians to embrace new moral priorities and responsibilities. He emphasizes the fact that wars often pose a grave threat to the existence and ethos of an entire nation. Gross argues that in response to this threat, nations and their citizens, including physicians, must shift their moral allegiance from the interests and rights of individuals to the interests and rights of the nation as a whole. This shift from individual to collective interests largely directs Gross’s answers to the moral questions he asks. He argues, for example, that military physicians must give priority to their own soldiers over enemy soldiers and civilians, and to soldiers who can be returned quickly to combat over soldiers with more severe injuries. He justifies this order of priority in part by asserting that military personnel lose their right to life. Gross concludes that physicians’ participation in torture is permissible if the torture is necessary to prevent imminent harm. He also asserts that physicians may have a duty to participate in weapons development, stating that “doctors must sometimes help build bombs.”

In *Bioethics and Armed Conflict*, Gross argues persuasively that the traditional guidelines for physicians in war are increasingly insupportable in today’s world of unconventional wars and weapons of mass destruction. However, Gross’s alternative, which subordinates the roles and responsibilities of military physicians to national interests, may swing too far in the opposite direction. It demands, at the least, a fuller description and defense of the moral authority of nation-states. Gross does acknowledge that the behavior of nations should conform to just-war principles and humanitarian law, but the role of these constraints remains unclear. The rules of the Geneva Conventions that protect the interests of noncombatants in wartime are certainly examples of humanitarian law, yet Gross contends that military physicians should not adhere to them. Despite these shortcomings, the arguments presented in this book pose a formidable challenge to physicians and scholars who would defend a more independent role for medicine in war.

John C. Moskop, Ph.D.
Brody School of Medicine at East Carolina University
Greenville, NC 27834
moskopj@ecu.edu

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**CORRECTION**

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Mono therapy (December 7, 2006;355:2427-43). Having discovered an error in their original reporting, the authors undertook a complete audit of all the data reported in the published article. The results of that audit change some of the published data, as follows. None of these changes materially affect the scientific findings, interpretation, or conclusions of the study. In the Methods section, the last sentence under Study Design (page 2428) should have read “Patients were followed until the termination of the study in June 2006, with a median treatment duration of 4.0 years (maximum, 6.1),” rather than “(maximum, 6.0).” In Table 1 (page 2430), in the “Time since diagnosis of diabetes” entry, the number of rosiglitazone patients should have been 651 for <1 year and 758 for 1–2 years. In the Results section, the first sentence under Secondary Outcomes (page 2433) should have read “The rate of progression to a confirmed fasting plasma glucose level of more than 140 mg per deciliter also differed significantly among the groups; 79 of 511 patients in the rosiglitazone group, as compared with 127 of 520 patients in the metformin group.”
(risk reduction, 36%; 95% CI, 15 to 52; P = 0.002)," rather than “risk reduction, 34.” In Figure 3 (page 2434), the ranges should have been as follows: Age: ≤50 yr, >50–60 yr, >60 yr; BMI: ≤30, >30–35, >35; Weight: ≤82.0 kg, >82.0–97.3 kg, >97.3 kg; Waist circumference: ≤99 cm, >99–110 cm, >110 cm; and Baseline fasting plasma glucose: ≤140 mg/dl, >140 mg/dl. The third sentence of the third paragraph under Secondary Outcomes (page 2434) should have read “From the longitudinal linear model, a mean glycated hemoglobin level of less than 7% was maintained until the visit at 57 months in the rosiglitazone group” rather than “60 months.” In Figure 4A (page 2436), the Treatment difference (95% CI) for rosiglitazone vs. metformin should have been −9.8 (−12.6 to −7.0). In Figure 4G (page 2437), the Annualized slope (95% CI) for rosiglitazone vs. metformin should have been 0.0010 (0.0006 to 0.0026) for metformin and 0.0011 (0.0007 to 0.0029) for glyburide. In the Discussion section, the third sentence of the second paragraph (page 2439) should have read “By comparing three drugs head to head, our study provides long-term evidence that progressive loss of glycemic control can be delayed and a mean glycated hemoglobin level of less than 7% for a longer period with rosiglitazone (57 months) rather than “60 months.” The second sentence of the fifth paragraph in the same section (page 2440) should have read “The protocol specified that all patients be free of known CHF on entry into the study. However, a retrospective review of source documents revealed that 17 patients (5 in the rosiglitazone group, 6 in the metformin group, and 6 in the glyburide group) entered the study with a current diagnosis of CHF. Only one of these patients (randomized to metformin) contributed to the events of CHF that are detailed in Table 2” rather than “At study entry, all patients were free of known CHF on entry into the study. In Table 2, ‘60 months.’ The second sentence of the fifth paragraph in the same section (page 2440) should have read “The protocol specified that all patients be free of known CHF on entry into the study. However, a retrospective review of source documents revealed that 17 patients (5 in the rosiglitazone group, 6 in the metformin group, and 6 in the glyburide group) entered the study with a current diagnosis of CHF. Only one of these patients (randomized to metformin) contributed to the events of CHF that are detailed in Table 2” rather than “At study entry, all patients were free of known CHF.” The article has been corrected on the Journal’s Web site at www.nejm.org.

**NOTICES**

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

**MEDICAL EDUCATION WEEK 2007**

The following workshops will be held in Singapore: “Workshop 1: On the Art of Listening” (April 23) and “Workshop 2: On the Skill of Mentoring” (April 24 and 25).

Contact Medical Education Week 2007, SGH Postgraduate Medical Institute, Singapore General Hospital, Block 6, Level 1, Outram Rd., Singapore 169608; or call (65) 6326 5284; or fax (65) 6223 9789; or see http://www.pgmi.com.sg; or e-mail chang.jingyun@sgh.com.sg.

**12TH CONGRESS OF THE EUROPEAN HEMATOLOGY ASSOCIATION**

The congress will be held in Vienna, June 7–10. Deadline for early registration is May 10.

Contact European Hematology Association Executive Office, Westblaak 71, 3012 KE Rotterdam, the Netherlands; or call (31) 10 436 17 60; or fax (31) 10 436 18 17; or e-mail info@ehaweb.org; or see http://www.ehaweb.org.

**ULTRASONOGRAPHY: COMPETENCE IN THE ICU**

The course will be offered in Orlando, FL, April 27–29.

Contact American College of Chest Physicians, 3300 Dundee Rd., Northbrook, IL 60062; or call (800) 343-2227; or e-mail accp@chestnet.org; or see http://www.chestnet.org/education/calendar.php

**STEM CELLS AND CNS REGENERATION**

The symposium will be held in Boston, May 31 and June 1. Deadline for submission of abstracts is April 30.

Contact Biosymposia, 1099 Hingham St., Rockland, MA 02370; or see http://www.biosymposia.org.

**SCIENTIFIC ADVANTAGE ANNUAL MSL LEADERSHIP SUMMIT**

The pre-meeting workshops and summit will be held in Bridgewater, NJ, on May 1 and 2, respectively.

Contact Arlene Vasquez, Scientific Advantage, 80 Morris-town Rd., #388, Bernardsville, NJ 07924; or call (908) 204-0995; or e-mail arlene.vasquez@scientificadvantage.com; or see http://www.scientificadvantage.com.

**AMERICAN SOCIETY OF BREAST SURGEONS**

The “8th Annual Meeting” will be held in Phoenix, AZ, May 2–6.

Contact the American Society of Breast Surgeons, 5950 Symphony Woods Rd., Suite 212, Columbia, MD 21044; or call (410) 992-5470; or fax (410) 992-5472; or e-mail meetings@breastsurgeons.org; or see http://www.breastsurgeons.org.

**HIV MANAGEMENT 2007: THE NEW YORK COURSE**

The course will be offered in New York, May 4 and 5.

Contact The New York Course, 430 Franklin Village Dr., Suite 105, Franklin, MA 02038; or call (888) 393-3996; or fax (508) 528-7880; or e-mail info@newyorkcourse.com; or see http://www.newyorkcourse.com.

**AMERICAN OCCUPATIONAL HEALTH CONFERENCE**

The conference will be held in New Orleans, May 5–8.

Contact American College of Occupational and Environmental Medicine, 25 Northwest Point Blvd., Suite 700, Elk Grove Village, IL 60007-1030; or call (847) 818-1800, extension 374; or fax (847) 818-9265; or see http://www.aoemo.org.

**NORTH CAROLINA OCCUPATIONAL SAFETY AND HEALTH EDUCATION & RESEARCH CENTER**

The following courses will be offered in Chapel Hill, NC: “Building Inspection and Management Planning for Asbestos” (refresher course, April 3); “Designing Asbestos Abatement Projects” (refresher course, April 4); “Certified Safety Professional (CSP) Review Course” (April 23–27); “Supervising Asbestos Abatement Projects” (April 30–May 4; refresher course, April 2); “COHN/Safety Management Certification Review Course” (May 7–10); and “Certified Hazardous Materials Manager (CHMM) Review” (June 18–21).

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

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A 33-YEAR-OLD WOMAN WITH A KNOWN BRCA1 MUTATION (2080DELA) WAS REFERRED FOR 3.0-TESSA MAGNETIC RESONANCE IMAGING (3T MRI). The patient’s mother had had breast cancer at the ages of 31 and 38 years; her sister had had breast cancer at the age of 30. Routine physical examination revealed no breast masses, and screening mammography showed extreme breast density but was otherwise normal. At follow-up approximately 4 months later, 3T MRI showed a progressively enhancing lesion, 1.6 by 1.0 cm (Panel A, arrow). Mammographic imaging showed new calcifications at the 10 o’clock position. A stereotactic biopsy was performed; 4 of 10 cores showed calcifications, and all cores showed ductal hyperplasia with no evidence of cancer. Approximately 1 year later, repeated 3T MRI showed a peripherally enhancing mass, 4.7 by 6.1 by 5.3 cm, extending to the pectoralis muscle, with extensive neovascularization (Panel B, arrow). A biopsy specimen showed the presence of an invasive adenocarcinoma of the breast, which was classified as grade II to III, with a negative test for estrogen receptor, at 0 fmol per milligram, and a borderline-positive test for progesterone receptor, at 13 fmol per milligram. The biopsy specimen was HER2/neu-negative and cytokeratin 5/6–positive, findings that were consistent with the presence of a basal-type breast cancer. The patient chose to receive further care from a local oncologist.

The BRCA1 mutation is associated with ovarian cancer as well as breast cancer. The sensitivity of mammography is decreased in women with high breast density. Therefore, close follow-up with more sensitive screening approaches, such as MRI, in women at high risk for breast cancer, such as those with the BRCA1 mutation, is warranted.

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