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Medicare keeps pace with patients’ needs, the addition of the drug benefit will help patients and doctors work together to alleviate symptoms and reduce the rate of complications of serious illness. We also expect the benefit to reduce the risk of related, catastrophic financial losses. The challenge is to ensure that these goals are achieved not only in 2006, but also for the foreseeable future.

As the Centers for Medicare and Medicaid Services developed the blueprint for the drug benefit, we first aimed to ensure that all beneficiaries, regardless of their health status or financial means, have access to high-quality, affordable drug coverage that keeps pace with current medical practice. Second, we aimed to provide continuous access to drugs needed by the chronically ill and third, to create a competitive, transparent marketplace offering a wide array of benefits to consumers.

Rigorous standards were set for health plans that wanted to participate. These standards mirror those that have worked to keep coverage up to date for employees and retirees of the federal government and for the millions of Americans who have health care coverage through their employers. Access to the benefit for people of limited means was made possible through both additional financial assistance and coordinated enrollment-focused outreach.

Persons who are also covered by Medicaid (“dual eligibles”) will pay no monthly premium or deductible, and their prescriptions will have copayments ranging from $0 to $5. Because these beneficiaries are on state Medicaid rolls, we have been able to enroll them automatically in plans in their regions to ensure that they will have uninterrupted comprehensive drug coverage. They can choose among alternative zero-premium plans at any time. We are also facilitating the enrollment of approximately 2 million more beneficiaries who are enrolled in the Medicare Savings Program, a limited form of Medicaid that does not include drug coverage, if they have not chosen a plan by spring 2006.

There are an additional 7 million beneficiaries with limited finances who may qualify for substantial extra assistance but who are hard to reach. We have been working with partners within the federal and state governments and...
within the health care community to provide as many means of contact and as much information as possible. Regional offices and partners have conducted more than 40,000 training sessions and presentations and have created 140 coalition networks with 10,000 volunteers. The www.medicare.gov Web site provides a variety of interactive tools and assistance, and a help line (1-800-MEDICARE) is staffed around the clock.

Formulary and other coverage requirements are designed to ensure that beneficiaries will have continuous access to medically necessary drug treatments, as required by law. For example, working with physicians and other health care providers, we identified six critical categories of drugs — antidepressants, antipsychotics, anticonvulsants, anticancer agents, immunosuppressants, and antiretroviral drugs for patients with HIV infection. For patients who require these drugs, therapeutic substitutions could be harmful, even over the short term. So all formularies include “all or substantially all” drugs in these categories, in addition to at least two drugs in every other therapeutic class.

We did not mandate that all formularies include all available drugs, because such a requirement would have limited the ability of plans to negotiate lower drug prices and therefore would have driven up beneficiaries’ costs. Instead, we required plans to make their coverage and costs clear to enrollees and to have a rapid appeals process for beneficiaries who need nonformulary drugs. Because of the combination of strict formulary oversight and strong competition among plans, both of which are necessary if the benefit is to be optimal, most plans are offering broad formularies. The vast majority include more than 80 of the 100 drugs most used by seniors.

In addition, we created what we hope will be a well-functioning market for prescription-drug coverage, where suppliers compete in terms of quality and price. We believe that such choices can work in health care, forcing competitors to reduce costs and offer better products in order to attract beneficiaries. But such competition requires careful ground rules, such as a high degree of transparency to facilitate informed choice, risk-adjusted government payments that level the playing field for plans that attract beneficiaries who have chronic illnesses, and formulary requirements ensuring that all plans are high quality.

There is already evidence that this market for prescription-drug plans is working, given the quality, cost, and range of offerings. For instance, the average premium and cost to the government of the drug plans offered for 2006 is 14 to 15 percent lower than the costs projected by independent experts: the average monthly premium is about $32, as compared with a projected $37; and the costs to the government are about $15 lower per month per beneficiary than was projected. In 49 of the 50 states, there is at least one plan with a premium of $20 per month or less. The lower prices reflect the discounted drug prices negotiated by the plans and other efficiencies achieved through partnerships and purchasing leverage. These savings are broadly available, so beneficiaries are not restricted to a single plan with a single formulary. For example, beneficiaries can choose a plan with an open formulary (which includes essentially all generic and brand-name drugs) or one with a closed formulary (which excludes some drugs). Plans with closed formularies tend to have lower premiums and more greatly discounted drug prices.

Competition has also resulted in better coverage options than those that would have been available if Congress had defined a specific coverage package rather than a minimum standard of coverage. Less than one third of both the prescription-drug plans and the Medicare Advantage plans use the standard benefit structure outlined in the Medicare law. In the standard structure, beneficiaries have a $250 deductible, pay 25 percent of their next $2,000 in drug costs, and then pay 100 percent of the next $2,850. At that point, catastrophic coverage begins, and beneficiaries pay only 5 percent of drug costs. But beneficiaries can instead choose plans with no deductible, plans with coverage for the $2,850 gap, or plans that offer drugs with different levels of copayments (tiered copayments). Tiered copayments are usually fixed, lower copayments (less than the 25 percent copayment in the standard benefit) for drugs that are inexpensive and designated as preferred drugs and higher copayments for drugs that are not included on a preferred list or for which there is a lower-cost generic form.

With these competitive choices, the prescription-drug benefit does not have to be one size fits all for Medicare’s diverse 42 million beneficiaries. But every plan must meet Medicare’s actuarial standards, provide access to medically necessary drugs, and protect against high drug costs. Beneficiaries can choose among plans according to their preferences and specific financial needs, using sev-
eral available tools. Medicare’s help line and Web site provide patients with personalized information on the costs of the plans and the drugs included in their formularies, and there are also numerous community resources and partners.

Some beneficiaries will have challenging questions and will probably turn to their physicians. They may start by asking physicians basic questions about coverage as they begin to consider their choices. In addition to referring patients and their caregivers to Medicare’s help line and Web site, physicians can get information on local advisers in their community through www.eldercare.gov, and they can get explanatory materials to distribute in their offices through www.cms.hhs.gov/medlearn/drugcoverage.asp.

Physicians are uniquely suited to helping their patients to review the medications they take and to identify plans that provide substantial savings on those or equivalent medications. Physicians will want to focus particularly on patients who are dually eligible and have been automatically enrolled in a plan but may wish to switch to another one.

Assistance is available to physicians (see table), including tools for the office and a brief course that can be taken for continuing medical education credit. The Formulary Finder at www.medicare.gov provides quick search capability, and the Prescription Drug Plan Finder provides cost information on all drugs used by a beneficiary. Medicare is also making the formulary information publicly available so that offerings can be incorporated into commercial formulary evaluation search tools.

Taking advantage of the new prescription-drug benefit will require some effort, but the effort will pay off for Medicare beneficiaries and their physicians. Improved access to prescription drugs will support physicians’ efforts to work with patients to prevent disease and its complications, and patients with limited means will no longer have to choose between their medications and other basic necessities. These critical improvements to Medicare are long overdue.

Dr. Bach is a senior adviser and Dr. McClellan the administrator of the Centers for Medicare and Medicaid Services, Washington, D.C.

### Resources Available to Physicians and Patients on the Medicare Prescription-Drug Benefit.

#### For the practice
- Materials for the office: Can be printed or ordered from www.medicare.gov and from numerous partner Web sites (e.g., www.aarp.org).
- Local informational resources: www.medicare.gov, www.eldercare.gov, or 1-800-MEDICARE.
- Continuing medical education credit: Available through the University of Kansas certificate program for $15.
- Practice tools: Available at www.cms.hhs.gov/medlearn/drugcoverage.asp.

#### About formularies
- Requirements: All are approved by the government, include a broad range of medically appropriate drugs to treat all diseases, and have mechanisms to allow all nonformulary drugs to be provided through a streamlined appeals and exceptions process.
- Direct comparison of local formularies: Available at www.medicare.gov.

#### For patients
- Financial help: Contact the Social Security Administration at www.ssa.gov/prescriptionhelp or 1-800-772-1213. An application is required.
- Decision support: Available at www.benefitscheckup.org.

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**Promise and Perils for Patients and Physicians**

Richard L. Kravitz, M.D., M.S.P.H., and Sophia Chang, M.D., M.P.H.

On January 1, 2006, the Medicare Prescription Drug Improvement and Modernization Act (MMA) will become a fact of life for 42 million Medicare beneficiaries and their physicians. For the past three months, America’s older citizens have been barraged with educational and marketing initiatives for various drug plans, though it has been an uphill battle: an October poll indicated that 61 percent did not understand the program “somewhat well” and 54 percent did not intend to sign up for coverage.1

The task of sorting through the myriad alternatives will fall square-ly on patients and their physicians. The federal government has posted comprehensive information on the Internet, and states are scrambling to offer consumer help lines and counseling. Physicians, however, will be on the front lines. All physicians who write prescriptions for Medicare beneficiaries
should familiarize themselves with the major components of the program and know where to get answers and advice.

Those who follow the federal legislative process know that political compromise often begets convoluted policy, but the Medicare drug benefit is particularly complex. Between November 15, 2005, and May 15, 2006, patients eligible for Medicare will have the opportunity to sign up for one of several prescription-drug plans (PDPs) offered in their states. These PDPs come in two varieties: stand-alone plans for those in fee-for-service Medicare and plans associated with a Medicare Advantage health maintenance or preferred-provider organization. Most states will have roughly 15 plans offered by private companies, all with different premiums, deductibles, copayments, coverage gaps, formularies, pharmacy networks, and geographic coverage. The plethora of choices will be a mixed blessing, because even when features are compared side by side, it will be difficult for beneficiaries to discern which plan (if any) best meets their needs.

Premiums are expected to average $33 per month nationwide, but most states will have at least one plan that charges less than $20 per month. (Premiums are expected to cover about 25 percent of the standard drug benefit, with the government contributing the rest.) The model plan entails a $250 deductible, followed by 75 percent coverage for the next $2,000 in total drug costs ($750 in total out-of-pocket costs), followed by the “doughnut hole” in which patients pay the next $2,850 in drug costs. Once a patient has spent $3,600 during a calendar year, the model plan, as outlined by Bach and McClellan in this issue of the Journal (pages 2733–2735), covers 95 percent of any further prescription-drug costs. Most of the plans differ somewhat from this model but offer benefits deemed to be “actuarially equivalent.” For example, 28 of 47 stand-alone plans in California will have no deductible, whereas others will plug the doughnut hole in exchange for a higher premium.

Adding to the confusion are several special cases. Beneficiaries who are eligible for both Medicare and Medicaid and who do not choose a drug plan will automatically be assigned to one on January 1, 2006. Other beneficiaries with few assets and low annual incomes can apply for extra financial assistance, including cost sharing and reductions in premiums and deductibles. This subsidy program is administered by the Social Security Administration. Patients who already have prescription-drug coverage (through a Medicare Advantage plan, a union, or an employer) may keep it if the benefits meet the government’s benchmark. If the coverage does not pass this test (most “Medigap” supplemental policies are expected to fail), subscribers are supposed to be notified and urged to choose a PDP. The potential for bureaucratic snafus seems endless.

To add a sense of urgency, there are penalties for late enrollment. Medicare beneficiaries who do not sign up for a drug plan by May 15, 2006, will have their future premiums increased by 1 percent for each month of delay. The rationale is to discourage seniors from enrolling in a PDP just as they begin to incur large drug costs — behavior that would distort the program’s insurance function and be fiscally unsound. So, for instance, a healthy 66-year-old man who currently takes no prescription drugs would have to pay up to 50 percent more in premiums if he waited until his diet-controlled diabetes suddenly required a multiple-drug regimen when he was 70. In most states, patients with current out-of-pocket expenses for prescription drugs of $50 per month will save only $100 to $200 annually by enrolling in a PDP (see table). The savings mount steeply as monthly outlays increase but could be offset by the “procrastination penalty.” In California, if our hypothetical 66-year-old man delayed enrolling in a PDP until his monthly drug costs rose to $100 in 2010, the anticipated savings of $458 in out-of-pocket expenses would be partially offset by a $198 annual increase in premiums (without inflation).

All plans will have a formulary — a list of covered drugs that may be tiered according to cost (usually generic, preferred brand-name, and nonpreferred brand-name drugs) and special requirements (e.g., prior authorization, step therapy, or limits on the number of pills prescribed). All formularies must include at least two agents per therapeutic category, but the categories are defined quite broadly (e.g., antiarrhythmic agents, inhibitors of the renin–angiotensin–aldosterone system, and oral hypoglycemic agents). Thus, many patients will find that some of their medications are not covered. Most will probably switch to an alternative agent, but some may abandon therapy altogether, with potentially serious clinical consequences. Seniors who find a plan that covers their entire regimen, minimizes out-of-pocket...
costs, and permits a continuing relationship with their corner pharmacy will have cause to celebrate. However, plans can change their formularies monthly, whereas most beneficiaries will be locked into their drug plan for the year. As a result, some patients will be forced to switch to alternative agents midyear or else pay more for the privilege of maintaining a stable regimen.

Whether physicians are ready to meet the challenge is uncertain, since surveys suggest that most are principally concerned with the clinical aspects of prescribing and have little interest in helping their patients navigate formularies and deal with drug costs.3,4 Pharmacists are arguably better positioned to help, but patients may inadvertently choose a plan that does not permit them to use their local pharmacy.

Physicians should consider the following advice as they help patients weigh their choices (see diagram). First, many elders will be confused to the point of panic, but they should avoid a rush to judgment. The initial enrollment period for the Medicare prescription-drug program extends through May 15, 2006. There is no time to waste but plenty of time to gather information and review options. Seniors who already have prescription-drug coverage under a Medicare Advantage, Medigap, employer, or union policy may be able to stay with their current plan, but they should get in touch with their plans to find out whether they pass the government’s equivalency test and will maintain drug coverage. Beneficiaries who remain with their current, approved plan will not be penalized if they move to a Medicare PDP later.

Second, most seniors will save

<table>
<thead>
<tr>
<th>State</th>
<th>Monthly Prescription-Drug Costs (Baseline)</th>
<th>Annual Prescription-Drug Costs (Baseline)</th>
<th>Annual Out-of-Pocket Expenses with Medicare Drug Benefit</th>
<th>Projected Out-of-Pocket Savings</th>
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<td>537</td>
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* Calculations were performed with the Medicare Cost Calculator, which generates estimates on the basis of each state’s lowest published monthly premium: California, $5.41; Colorado, $8.62; Michigan, $13.75; South Carolina, $16.75; Massachusetts, $7.32.
money by enrolling in a PDP. However, the greatest benefit of the program is insurance against catastrophic drug costs. For seniors with monthly prescription-drug expenses of less than $250, the net savings will not be dramatic. The major benefits will accrue to those with drug expenses of $1,000 per month or more (see table).

Third, in selecting a PDP, patients should consider the three Cs: cost, coverage, and continuity. Plans will vary in terms of the monthly premium, the deductible and copayment structure, the drug formulary, and contractual relationships with pharmacies. Patients who are inclined to resist a switch from atorvastatin to simvastatin or from their local pharmacy to a chain pharmacy may have to pay a bit more to keep taking the same drug dispensed by the same pharmacist. In selecting a Medicare Advantage plan with prescription-drug coverage, patients should also pay attention to hospitalization copayments, since these may go unnoticed when comparing drug coverage alone.

Physicians should be prepared to advocate for their patients.
quests for coverage of medications other than those in the formulary can be initiated by the patient or the physician, and plans are supposed to respond within 72 hours (or 24 hours for expedited requests). Appeals are permitted but may be time-consuming. Physicians may also request exceptions to the tiered cost-sharing structure if, for example, their patient cannot tolerate a generic drug. The capacity of many frontline physicians to deliver on these new responsibilities is uncertain, especially given the harried pace and poor reimbursement that are associated with primary care practice. The MMA has no provision for compensating physicians or their office staff for undertaking these activities.

Although there is turbulence ahead, physicians and patients should remember that they are not alone. At last count, the Medicare Web site listed 280 frequently asked questions, and help is available through regional senior health insurance assistance programs and area agencies on aging (www.aoa.gov/eldfam/how_to_find/agencies/agencies.asp).

The new prescription-drug benefit represents the biggest change in Medicare since its inception in 1965. In the short term, the success of the benefit will hinge on whether patients can successfully negotiate its convoluted options and rules. Over the long haul, the program’s viability will depend on whether expenses for prescription drugs can be brought under control. New drug discoveries during the next 10 years promise to deliver remarkable benefits—at startlingly high prices. No doubt the Medicare drug benefit will change over time, and physicians will continue to be called on to help patients traverse the shifting policy landscape safely and successfully.

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MEDICARE DRUG BENEFIT

Benefits and Consequences for the Poor and the Disabled


The new Medicare Part D will improve access to medications for millions of Americans. One subgroup of beneficiaries, however, may inadvertently be made worse off: the 7.2 million people enrolled in both Medicaid (because they are poor) and Medicare (because they are elderly or disabled). These beneficiaries, known as the dually eligible, already receive drug benefits through state-run Medicaid programs; but as of 2006, they will be required to enroll in Medicare Part D.

Moving the dually eligible recipients of drug benefits to new federal programs raises several concerns: these beneficiaries may have problems making the transition and negotiating the system; they may discontinue use of essential medications because of increased cost sharing; they may need to switch medications because their new plan offers different coverage from their old one; and they may have difficulty obtaining essential medications because of formulary restrictions.

The dually eligible are poorer and sicker than other Medicare patients (83 percent report fair or poor health vs. 57 percent of those who are not dually eligible), have a higher rate of mental illness or dementia (33 percent vs. 12 percent), are less educated (40 percent have graduated from high school vs. 75 percent), are more likely to be members of minority groups (43 percent vs. 16 percent), and are more likely to live in a nursing home (19 percent vs. 3 percent). Of the country’s 1.6 million nursing-home residents, 70 percent are dually eligible, and most take multiple medications.

Medicare will pay the entire Part D premium for the dually eligible (see table), who will not be required to pay the standard $250 deductible, the $500 in coinsurance for the first $2,250 in drug benefits, or the next $2,850 of drug costs. The Center for Medicare and Medicaid Services (CMS)
began sending letters to dually eligible patients in November, detailing the impending change in their drug coverage and informing them that they will be automatically enrolled in a drug plan if they do not select one by December 31, 2005.

But they were given only six weeks to enroll in a Medicare plan — a selection process that can take several months — despite the fact that this group is especially difficult to reach and to educate about coverage changes. Particularly at risk are the 2.4 million patients with dementia or psychiatric illnesses, who may have difficulty negotiating the system, and patients who move from the community into a nursing home, where they will probably have to select from a whole new set of plans.

Patients who are automatically enrolled in a plan on January 1 and would like to choose a different plan will be permitted to switch. There is no established strategy, however, for moving patients smoothly from one plan to another. Some will be required to switch to different medications covered by the new plan, and some may experience new side effects from new drugs, while others may stop taking their medication altogether.

Before the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003, the Medicaid prescription-drug benefit provided to the dually eligible was generally comprehensive and involved minimal copayments, except in the 12 states that cap the number of prescriptions allowed (see table). For dually eligible patients who already receive comprehensive drug benefits, the MMA will increase financial barriers and reduce access in most states. These patients will be responsible for copayments of $1 to $2 for generic drugs and $3 to $5 for brand-name drugs, instead of the typical copayment of $3 or less or even no fee under Medicaid. Medication costs should be reduced for patients living in states with drug caps, if their drug use exceeds the cap. But in other states, it is not clear that costs will be reduced. Patients who are chronically mentally ill are particularly susceptible to increases in copayments that are as low as $1.

Although the CMS requires formularies to include “all or substantially all” antidepressant, antipsychotic, anticonvulsant, immunosuppressant, antineoplastic, and antiretroviral agents in 2006, since therapeutic substitution in these classes of drugs is generally inappropriate, this policy will be reevaluated for 2007. The CMS will also require drug plans to fill prescriptions, for an undefined transitional period, for dually eligible nursing-home patients who are currently on stable medication regimens.

However, there may be reduced coverage or none at all for a small number of effective drugs. For example, the specific exclusions of benzodiazepines and opiates such as buprenorphine are of great concern. Oral benzodiazepines are listed on the World Health Organization’s Essential Drugs List for

### Prescription-Drug Coverage for the Dually Eligible under Medicare Part D and State Medicaid Programs.©

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Medicaid (Full Benefits for the Dually Eligible)</th>
<th>Medicare Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copayment</td>
<td>None, in 10 states; in other states, ranges from $0.50 to $3.00, depending on state, type of drug (brand-name vs. generic), and patient income.</td>
<td>$1 for generic, $3 for brand-name drugs, if patient’s income is below the federal poverty level; $2 for generic, $5 for brand-name drugs, if income is above the federal poverty level; none if catastrophic limit has been reached.†</td>
</tr>
<tr>
<td>Prior approval</td>
<td>Required in 35 states for selected “high-cost” drugs, which vary from state to state.</td>
<td>Not needed for “all or substantially all” drugs in the following classes: antidepressant, antipsychotic, anticonvulsant, immunosuppressant, antineoplastic, and antiretroviral agents in 2006 (to be reevaluated in 2007); may be required for selected drugs in other classes, depending on the individual plan.</td>
</tr>
<tr>
<td>Coverage limitation</td>
<td>In 12 states, cap on the number of prescriptions beneficiaries may fill each month; cap ranges from 3 (Arkansas, Nevada, and Oklahoma) to 10 (West Virginia) per month.</td>
<td>No monthly cap.</td>
</tr>
</tbody>
</table>

© Data are from the Kaiser Commission on Medicaid and the Uninsured. ² There are 51 Medicaid programs — 1 for each of the 50 states and 1 for the District of Columbia.

† The catastrophic limit is the highest amount of combined out-of-pocket copayments and CMS drug reimbursements for services covered under Part D during the course of one year — or $3,600.
anxiety and sleep disorders and are also indicated for the short-term management of bipolar disorders and for treatment of panic attacks that have been refractory to antidepressants. The loss of coverage may result in the abrupt cessation of benzodiazepine therapy in as many as 1.7 million long-term users, potentially leading to severe or even life-threatening withdrawal symptoms.

To address this problem, Representatives Benjamin Cardin (D-Md.) and Jim Ramstad (R-Minn.) have filed legislation to cover benzodiazepines. If this bill is not passed, the CMS has indicated that states should cover drugs excluded by Medicare Part D if they are covering such drugs for other Medicaid enrollees. It is not yet clear, however, how many states will cover such drugs for dually eligible patients on January 1.

Private Medicare drug plans, which will decide which medications are included in their formularies, are permitted to restrict coverage to two drugs per “class.” The U.S. Pharmacopeia classifications have been criticized for being too broad, thus defining an inadequate number of classes; for example, all newer and older oral hypoglycemic agents constitute a single class. Medicare’s acceptance of these classifications allows plans to restrict the total number of drugs covered, perhaps incorrectly assuming equivalence within a class. Aside from the designated classes in which therapeutic substitution is least appropriate, it is unclear how extensive the options will be overall.

Proposed plans vary in medication coverage, and many rely on utilization-management techniques. Dispensing of some agents may be allowed only after the failure of “preferred” agents or prior authorization for use of “non-preferred” drugs. Moreover, “off-label” prescribing is not reimbursable under Medicare, which may be relevant if prior authorization is required. To minimize adverse events, clinicians will need to carefully monitor chronically ill patients who are forced to switch to a new medication.

Research has demonstrated that policies that increase cost sharing for medications reduce the use of essential medicines such as thiazide diuretics, antidiabetes agents, and psychotropic agents, even as they reduce inappropriate drug use. Such policy changes may lead to negative health outcomes and increased use of emergency services and overall health care costs. A number of steps could maximize the benefits of the MMA for the dually eligible. We believe that the transition period should be lengthened to at least one year, creating a long “crossover” period during which beneficiaries can continue to obtain their medication through Medicaid. The CMS should identify explicitly who is to coordinate this transition. Prescribers should be supported by state-led prescribing-education programs to improve their awareness of intraclass variation in the effectiveness and side effects of specific drugs and to ensure that required medication switches do not compromise safety. Finally, the CMS should commission rapid studies to examine the impact of formulary restrictions and changes in cost sharing on the use of essential medication and health outcomes and should modify policies that cause underuse of essential medications or deleterious health effects.

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A Beneficial Side Effect of the Medicare Drug Benefit

Richard Platt, M.D., and Alexander Ommaya, Sc.D.

A

n unintended effect of the Medicare Part D benefit could be the creation of the world’s most valuable resource for understanding how drugs are used, especially by the elderly and the chronically ill, and their risks and benefits. This resource would be created by linking information on drug dispensing to patients’ other health information. Medicare data are available for more than 40 million people. These data can transform our ability to assess drugs under real-life conditions, particularly in this vulnerable population, which is often underrepresented in clinical trials. However, in order to realize this benefit, we must make it a priority, justify it to the public, and provide adequate funding.

To understand the opportunity before us, it helps to understand how little we know now. The Food and Drug Administration (FDA) often approves a drug for long-term use on the basis of minimal long-term safety data: as few as 100 people may have been followed for adverse effects in studies lasting at least one year. Furthermore, the FDA rarely can compel manufacturers to conduct postapproval studies. The current mainstay for drug safety is the spontaneous reporting of adverse events to the FDA’s MedWatch program, which suffers from underreporting, variable data quality, and the lack of a mechanism to assess confounding risk factors. Spontaneous reports are a particularly poor instrument for detecting increased risks of common conditions, such as cardiac disease, that greatly affect public health.

The lack of systematic collection and analysis of post-marketing data on the use of drugs and the outcomes of treatment has delayed the discovery of some serious problems until after millions of people have been exposed. For example, cisapride (Propulsid) was withdrawn because it had been prescribed to many people with contraindications, and several coccibes are now known to increase the risk of myocardial infarction.

Two existing programs share features that can be adopted for Medicare data. First, the Vaccine Safety Datalink Project of the Centers for Disease Control and Prevention, which involves the use of linked data from health plans, is an invaluable source of data on vaccine safety. Second, the FDA makes some use of linked pharmacy and administrative records from health plans. These databases identify everyone who is eligible to receive a drug or vaccine, the starting and stopping dates of administration, and many outcomes and coexisting medical conditions. In addition to being useful for safety studies, these data sometimes allow assessment of the effectiveness of different therapies under conditions of actual use.

There are important limitations to these data, however. They do not identify some conditions with sufficient specificity, contain no information on actual drug ingestion, lack important information such as smoking status and body-mass index, often lack historical information, and include only drugs covered by the health plan. Therefore, it is important to review patients’ full medical records in the small number of cases in which this information is critical.

Some prerequisites already exist for using Medicare data linked with data from health plans to study the use, risks, and benefits of drugs. Most important, the Centers for Medicare and Medicaid Services (CMS) has proposed linking Medicare drug claims with diagnosis and procedure claims. In addition, the FDA has experience in working with linked data and in collaborating with expert groups such as the Centers for Education and Research on Therapeutics (funded by the Agency for Healthcare Research and Quality and administered by that agency in collaboration with the FDA).

To take advantage of the opportunity at hand, the CMS must carry out its proposal of creating a fully linked data set and ensure that it remains current. The CMS, the FDA, and their designees will need the ability to review selected outpatient and inpatient records. These agencies will need to clarify their authority to perform these reviews and explain their purpose satisfactorily to clinicians and patients. Finally, the FDA and other agencies will need new sources of funding if they are to use this information meaningfully and to conduct research on new methods.
for using it optimally. Additional issues, such as a means of sharing these data with researchers and others, must also be addressed.

Medicare data will offer a great opportunity to improve our ability to understand the balance of benefits and risks of drug treatment. If we take advantage of this opportunity, we will know much more about whether drugs are used as intended, whether they have their intended effects, and how risky they are.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Institute of Medicine.

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An interview with Dr. Arnold Epstein about the Medicare prescription-drug benefit may be heard at www.nejm.org. Dr. Epstein is a professor of health care policy at the Harvard School of Public Health, a professor of medicine at Harvard Medical School, and an associate editor of the Journal.

F O C U S  O N  R E S E A R C H

Preparing Stroke in Sickle Cell Anemia
Orah S. Platt, M.D.

In the late 1930s, William Bosworth Castle and his colleague Thomas Hale Ham were studying blood samples obtained from patients with sickle cell anemia and found that the viscosity of the blood increased dramatically as its oxygen content decreased. As Castle later reflected, “It immediately occurred to us that this was because the elongated, sickled red cells had become tangled up ‘like haywire.’” Castle and Ham went on to hypothesize about the pathophysiology of organ damage in sickle cell anemia in a way that still drives much of our thinking today: “a vicious cycle of erythrostasis may be set up because the critical oxygen tension for a marked increase of sickling is relatively close to that of the normal venous blood.” This hypothesis predicts that as red cells become deoxygenated in the capillaries, the sickle hemoglobin inside them polymerizes, decreasing the cells’ ability to squeeze through the capillaries in single file. Blood flow stops, and the surrounding tissues become ischemic.

The hypothesis makes sense for tissues such as the spleen and marrow, where the blood flow is sluggish, oxygen tension is low, and the vessels are small. It does not, however, explain acute cerebral infarction — one of the most devastating complications of sickle cell anemia. Stroke in sickle cell anemia occurs in about 11 percent of patients under 20 years of age. The major symptom is sudden hemiparesis with or without aphasia, and the most common finding is obstruction of a distal intracranial internal carotid artery or a proximal middle cerebral artery. These vessels are relatively large, with diameters that are normally measured in millimeters. Oxygenated blood pulses through them with velocities of hundreds of centimeters per second. The question is, How can micron-scale red cells acutely occlude a millimeter-scale artery, especially at the low hematocrit that is typical of patients with sickle cell anemia? The answer is that the arteries themselves are not normal.

Adams and colleagues have pioneered the use of transcranial Doppler ultrasonography to study the blood supply of the brain in children with sickle cell anemia. They discovered that 10 percent of children without neurologic signs or symptoms had abnormal blood-flow velocities, indicative of clinically significant arterial stenosis. If left untreated, these patients have a relative risk of stroke of approximately 40. Postmortem examination of cerebral artery stenoses in such patients reveals proliferative intimal hyperplasia reminiscent of the inflammatory vascular lesions seen in other diseases. The genesis of these lesions is probably related to the well-described tendency of sickle cells to adhere to, activate, and damage endothelial cells.

An important early event (depicted in the diagram) is the at-
Cerebral Artery Damage and Healing in Sickle Cell Anemia.

In sickle cell anemia, cerebral artery damage results as sickle reticulocytes and more mature red cells bind to endothelial cells through specific ligands and are exposed to oxidants, causing these cells to be activated (Panel A). Activated endothelial cells become increasingly adhesive for red cells, white cells, and platelets, and some are dislodged from the underlying matrix (Panel B). As more cells adhere and are activated, a “cloud” of inflammatory mediators, chemoattractants, adhesion molecules, growth factors, procoagulants, and free hemoglobin is produced. Smooth-muscle cells migrate and proliferate, causing a hyperplastic lesion that encroaches on the artery lumen (Panel C). Ultimately this lesion, although asymptomatic, becomes detectable on transcranial Doppler ultrasonography (Panel D). A transfusion regimen, by keeping the production of sickle cells to a minimum, prevents acute sickling and stroke (Panel E) and promotes the reversal of injury to the vessel. When transfusion is discontinued, the lesion (and the risk of stroke) recurs.

attachment of a particularly sticky, oxidant-generating sickle reticulocyte to an endothelial cell in the turbulent environment of the carotid artery circulation. The encounter activates and damages the endothelial cell, stimulating endothelial cells and white cells to produce inflammatory cytokines, chemoattractants, adhesion molecules, procoagulants, and growth factors. White cells and platelets also adhere, amplifying endothelial-cell activation and aggravating the inflammatory process. Some activated endothelial cells detach from the vessel wall and circulate freely. With time and sufficient stimulation, smooth-muscle cells in the blood vessel migrate into the wall, proliferate, and narrow the arterial lumen.

Transcranial Doppler ultrasonography can detect an expanding lesion, one that is large enough to put the patient at high risk for
acute arterial obstruction. The coup de grace — stroke — occurs when the tipping point is reached in the delicate relation between oxygenation and perfusion on the one hand and inflammation and coagulation on the other — when deoxygenated red cells containing polymerized sickle hemoglobin get caught up in the damaged vessel and obstruct the blood flow. This process is further complicated by the release of free hemoglobin from fragile sickle cells, which effectively quenches locally produced nitric oxide that could have stimulated a beneficial vasodilation.

Adams and colleagues have shown that if children with stenotic cranial-artery lesions, as demonstrated on transcranial Doppler ultrasonography, are maintained on a regular program of transfusion that is designed to suppress erythropoiesis so that no more than 30 percent of their circulating red cells were their own, about 90 percent of strokes in such children could be prevented. In their follow-up study, reported in this issue of the Journal (pages 2769–2778), they find that a high risk of stroke returns after transfusion is discontinued. It appears that transfusion does not simply prevent stroke but actually reverses the stenotic lesion — on Doppler studies, blood-flow velocities return to normal. Apparently, during the period of the transfusion regimen the reduction in the lesion-forming mechanism was sufficient to allow at least some repair to occur.

We know from studies of siblings that there is a genetic component to the risk of stroke in sickle cell anemia. There is also a genetic component to the risk of stroke in the general population. Given the overlap in the possible mechanisms underlying vascular injury in stroke related to sickle cell disease and stroke in general, it is not surprising that the same candidate genetic contributors to stroke in both populations have become of interest. I anticipate that the search for predictive genetic profiles will yield new ways to identify children with sickle cell anemia who are at high risk of stroke and to help tailor more specific treatment for them. In the meantime, it will be critically important that all children with sickle cell anemia have easy access to transfusion and to routine transcranial Doppler screening and follow-up so that in these children most strokes can be avoided.

Dr. Platt reports having received royalties on a patent for a Gardos channel blocker.

Dr. Platt is chief of the Department of Laboratory Medicine at Children’s Hospital Boston and master of the William B. Castle Society at Harvard Medical School — both in Boston.

**THIS WEEK in the JOURNAL**

**ORIGINAL ARTICLE**

**Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer**

In a randomized comparison of letrozole with tamoxifen for the adjuvant treatment of early-stage, hormone-receptor–positive breast cancer in more than 8000 postmenopausal women, disease-free survival was significantly longer in the letrozole group. The five-year survival rates were 84.0 percent in the letrozole group and 81.4 percent in the tamoxifen group.

SEE P. 2747; EDITORIAL, P. 2807; CME, P. 2830

**ORIGINAL ARTICLE**

**Rescue Angioplasty or Repeated Thrombolysis after Failed Thrombolytic Therapy**

In this multicenter trial, patients in whom thrombolytic therapy for acute myocardial infarction failed were randomly assigned to repeated thrombolysis, conservative therapy, or emergency percutaneous coronary intervention (rescue PCI). Event-free survival was better among patients assigned to rescue PCI.

SEE P. 2758; CME, P. 2831

**ORIGINAL ARTICLE**

**Prophylactic Transfusion to Prevent Stroke in Children with Sickle Cell Disease**

Prophylactic transfusions have been shown to prevent stroke in children with sickle cell disease, but at the risk of iron overload. This trial of transfusion cessation in children with sickle cell disease who were not considered to be at high risk for stroke showed that cessation was associated with either Doppler blood-flow recordings suggesting a high risk of stroke or stroke itself.

SEE P. 2769; PERSPECTIVE, P. 2743

**SPECIAL ARTICLE**

**Registration at ClinicalTrials.gov between May and October 2005**

As of September 13, 2005, the International Committee of Medical Journal Editors has required that all trials submitted for publication be registered in a public database. This study examines the records registered in ClinicalTrials.gov from May 11 to October 11, 2005. The number of trials in the database approximately doubled, and the information about the trials became more specific.

SEE P. 2779; EDITORIALS, P. 2809 AND P. 2811

**CLINICAL PRACTICE**

**Acute Pulmonary Edema**

A 62-year-old man presents with a three-day history of progressive dyspnea, nonproductive cough, and low-grade fever. His blood pressure is 100/60 mm Hg, his heart rate 110 beats per minute, his temperature 37.9°C, and his oxygen saturation while breathing room air 86 percent. Chest auscultation reveals rales and rhonchi bilaterally. A chest radiograph shows bilateral pulmonary infiltrates consistent with pulmonary edema and borderline enlargement of the cardiac silhouette. How should this patient be evaluated to establish the cause of the acute pulmonary edema and to determine appropriate therapy?

SEE P. 2788; CME, P. 2829

**CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL**

**A Man with a One-Month History of Nontender Left Mandibular Swelling**

An 18-year-old man reported gradual painless swelling of the left mandible that had occurred over one month. An examination showed enlargement of the left mandible, with normal dentition. Imaging studies revealed a large, cystic lesion in the ramus and body of the left mandible. A diagnostic and therapeutic procedure were performed.

SEE P. 2798
A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer

The Breast International Group (BIG) 1-98 Collaborative Group*

ABSTRACT

BACKGROUND
The aromatase inhibitor letrozole is a more effective treatment for metastatic breast cancer and more effective in the neoadjuvant setting than tamoxifen. We compared letrozole with tamoxifen as adjuvant treatment for steroid-hormone-receptor–positive breast cancer in postmenopausal women.

METHODS
The Breast International Group (BIG) 1-98 study is a randomized, phase 3, double-blind trial that compared five years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor–positive breast cancer: letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole. This analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially; events and follow-up in the sequential-treatment groups were included up to the time that treatments were switched.

RESULTS
A total of 8010 women with data that could be assessed were enrolled, 4003 in the letrozole group and 4007 in the tamoxifen group. After a median follow-up of 25.8 months, 351 events had occurred in the letrozole group and 428 events in the tamoxifen group, with five-year disease-free survival estimates of 84.0 percent and 81.4 percent, respectively. As compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease-free survival (hazard ratio, 0.81; 95 percent confidence interval, 0.70 to 0.93; P = 0.003), especially the risk of distant recurrence (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; P = 0.001). Thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and cardiac events and of hypercholesterolemia.

CONCLUSIONS
In postmenopausal women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites. (ClinicalTrials.gov number, NCT00004205.)
ADJUVANT ENDOCRINE THERAPY WITH tamoxifen significantly prolongs disease-free and overall survival in postmenopausal women with early-stage breast cancer. Five years of treatment with tamoxifen reduces the risk of breast-cancer recurrence by 47 percent and the risk of death by 26 percent among patients with hormone-receptor–positive breast cancer. Despite these benefits, about half the women so treated relapse. Tamoxifen treatment is associated with rare but serious adverse effects, including endometrial cancer and thromboembolism.

In contrast to tamoxifen, which inhibits the activity of estrogen by competitively binding to the estrogen receptor, aromatase inhibitors block the conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma. Third-generation aromatase inhibitors include the nonsteroidal inhibitors letrozole and anastrozole and the steroidal inhibitor exemestane. With daily oral administration, anastrozole and exemestane inhibit aromatase activity in vivo by 97 to 98 percent and letrozole inhibits aromatase by more than 99 percent.

As first-line treatment for metastatic breast cancer, third-generation aromatase inhibitors are equivalent or superior to tamoxifen. Women with metastatic breast cancer who were given letrozole as first-line treatment had a significantly higher response rate, a significantly longer time to progression, and a significant improvement in one- and two-year survival rates, as compared with women given tamoxifen. Among women with early-stage breast cancer who were free of disease after five years of initial tamoxifen therapy, extended adjuvant therapy with letrozole improved disease-free survival and was superior to tamoxifen as neoadjuvant therapy.

Recent reports of large trials indicate a better outcome among women given aromatase inhibitors than among those given tamoxifen in the adjuvant setting. The Breast International Group (BIG) 1-98 study compared not only letrozole monotherapy with tamoxifen monotherapy as initial adjuvant endocrine therapy but also sequential treatment with the two agents in either order in postmenopausal women with hormone-receptor–positive breast cancer.

STUDY DESIGN
BIG 1-98 is a randomized, phase 3, double-blind trial involving postmenopausal women with operable invasive breast cancer that was positive for estrogen receptors, progesterone receptors, or both. The women were randomly assigned to receive monotherapy with letrozole or tamoxifen for five years, letrozole for two years followed by tamoxifen for three years, or tamoxifen for two years followed by letrozole for three years. From March 1998 to March 2000, 1835 women were randomly assigned to monotherapy with either letrozole (2.5 mg daily) or tamoxifen (20 mg daily). From April 1999 to May 2003, an additional 6193 women were randomly assigned to one of the four groups (the CONSORT flow chart of the BIG 1-98 trial is shown in Fig. 1 in Supplementary Appendix 2, available with the full text of this article at www.nejm.org). Randomization was performed with the use of permuted blocks and was stratified according to the participating center and according to whether chemotherapy was neither given nor planned, was completed before randomization, or was planned to be given concurrently with endocrine therapy.

This protocol-specified primary analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially. For this analysis, we included events and follow-up in the sequential-treatment groups that occurred up to 30 days after treatments were switched with events and follow-up in the monotherapy groups to increase the statistical power of the comparison of letrozole with tamoxifen. We also performed supplementary analyses comparing the monotherapy groups alone. The primary end point was disease-free survival, defined as the time from randomization to the first of one of the following events ending disease-free survival: recurrence at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second, nonbreast cancer; or death without a prior cancer event. Protocol-specified secondary end points included overall survival, defined as the time from randomization to death from any cause;
survival free of systemic disease (systemic disease–free survival), defined as the time from randomization to systemic recurrence (excluding local and contralateral-breast events), the occurrence of a second, nonbreast cancer, or death from any cause; and safety. Three additional end points that were not specified in the BIG 1-98 protocol were defined in the statistical-analysis plan because they were used as end points in other recently reported studies of aromatase inhibitors: disease-free survival as defined above, but excluding second, nonbreast cancers; the time to recurrence, defined as disease-free survival, but excluding second, nonbreast cancers and censoring data on patients who died without a recurrence of breast cancer; and the time to distant recurrence, defined as the time from randomization to the first recurrence at a distant site.

The study was coordinated by the International Breast Cancer Study Group (IBCSG), which was responsible for the study design, data collection and management, medical review, data analysis, and reporting (including the decision to publish). The ethics committees and required health authorities of each participating center approved the study protocol, and all patients gave written informed consent. In addition to the two planned interim analyses after the occurrence of 261 and 433 disease-free–survival events and the final efficacy analysis after 779 events, the IBCSG Data and Safety Monitoring Committee reviewed safety semiannually throughout the trial. Novartis, the manufacturer of letrozole (Femara), distributed the study drugs, provided financial support, and imposed no restrictions on the investigators with respect to trial data. The IBCSG Statistical Center had unblinded access to the database, and the IBCSG Data Management center had blinded access to the database. After the release of the results by the Data and Safety Monitoring Committee, the unblinded database was transferred to Novartis for the preparation of the clinical study report for health authorities. The manuscript was prepared by the Writing Committee, whose members made final decisions about content, and the Steering Committee (including employees of Novartis) reviewed the article and suggested changes. The Steering Committee chair (Dr. Thürlimann) vouches for the accuracy and completeness of the data.

**STUDY POPULATION**

Patients were eligible for the study if they were postmenopausal and had tumors that were positive for estrogen receptors, progesterone receptors, or both (definitions are provided in Fig. 1 of Supplementary Appendix 2). Primary surgery with resulting clear margins and adequate hematologic, renal, and hepatic function were required. Exclusion criteria included evidence of metastatic disease; previous or concurrent cancer other than adequately treated noninvasive breast or cervical cancer or basal-cell or squamous-cell carcinoma of the skin within 5 years before randomization; receipt of adjuvant antiestrogen therapy for the primary breast cancer for at least 1 month; and treatment with systemic investigational drugs within 30 days before randomization or topical investigational drugs within 7 days before randomization. The use of topical estrogens was discouraged during the trial. Before randomization, 2.1 percent had received neoadjuvant chemotherapy, 0.4 percent had received endocrine therapy for no longer than four months, and 39.3 percent had received hormone-replacement therapy more than four weeks before randomization (19.0 percent had done so within three months before randomization).

**STUDY PROCEDURES**

History taking and physical examination were performed at baseline, semiannually for the first five years, and yearly thereafter. Total cholesterol (90.8 percent of the values were not obtained after an overnight fast) was measured at baseline, semiannually for the first three years, yearly for the following two years, and one year after treatment ended. Hematologic and blood chemical measurements and bilateral mammograms were obtained at baseline and when medically indicated. Specific adverse events, which were listed on the case-report forms and graded according to the Common Toxicity Criteria of the National Cancer Institute (version 2) at each study visit during treatment, included myocardial infarction, cerebrovascular accident or transient ischemic attack, angina requiring percutaneous transluminal coronary angioplasty, angina requiring coronary-artery bypass grafting, a thromboembolic event, other cardiovascular events, hypercholesterolemia, bone fracture, vaginal bleeding, nausea, vomiting, hot flashes, and night sweats. Other adverse events
were also recorded but were not specifically listed on the case-report forms. Serious adverse events were reported in an expedited fashion. Efficacy analyses were conducted on the basis of data received as of November 12, 2004. In March and April 2005, two senior oncologists at the IBCSG Coordinating Center conducted a medical review of all cardiovascular events of grade 3,
4, or 5 and other adverse events of grade 3, 4, or 5 that were considered clinically relevant but whose cause was unclear (affecting 538 patients), and all deaths of women who had had no prior cancer-related event (93 patients). Changes resulting from the medical review, all of which were agreed to by the investigators as required by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use under its Good Clinical Practice guidelines, were included in the safety analysis.

**Efficacy**

Disease-free survival was significantly greater in the letrozole group than in the tamoxifen group (hazard ratio for the primary end point, 0.81; 95 percent confidence interval, 0.70 to 0.93; \( P = 0.003 \) by the log-rank test) (Fig. 1), especially reducing recurrence at distant sites (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; \( P = 0.001 \) by the log-rank test). The five-year estimates of disease-free survival were 84.0 percent in the letrozole group and 81.4 percent in the tamoxifen group (Fig. 1). Efficacy end-point events are shown in Table 2. A beneficial effect of letrozole was
also seen in analyses comparing the two mono-
therapy groups (data not shown).
Letrozole significantly reduced the cumulative
incidence of breast-cancer relapse as compared
with tamoxifen. This difference became evident
one year after randomization, and there was an
absolute difference of 3.4 percentage points at
five years (Fig. 2A). The cumulative incidence of
second, nonbreast cancers did not differ signifi-
cantly between the letrozole and tamoxifen groups
(Fig. 2B). The cumulative incidence of death among
women without a prior cancer event was higher
in the letrozole group than in the tamoxifen
group, but not significantly so (Fig. 2C).
Prospectively planned subgroup analyses of
disease-free survival showed a greater effect of
letrozole than of tamoxifen among patients who
received chemotherapy, those who did not receive
radiotherapy, and those with involved axillary
lymph nodes (Fig. 3). For example, the five-year
disease-free survival rate among patients with
node-positive cancer was 77.9 percent in the let-
rozole group and 71.4 percent in the tamoxifen
group; the value among patients with node-nega-
tive cancer was 88.7 percent in both groups. The
beneficial effect of letrozole on disease-free sur-
vival was similar for all combinations of estro-
gen-receptor and progesterone-receptor status
(Fig. 3).
Analysis of the secondary protocol-defined end
points of overall survival and systemic disease–free
survival also favored letrozole. Fewer women died
in the letrozole group than in the tamoxifen group
(166 patients [4.1 percent], as compared with 192
patients [4.8 percent]), but the overall survival did
not differ significantly between groups. Figure 3
shows the hazard ratios for the three additional
end points (disease-free survival, excluding sec-
ond, nonbreast cancers; time to recurrence; and
time to distant recurrence) in the letrozole group
as compared with the tamoxifen group.
SAFETY
More patients in the letrozole group than in the
tamoxifen group reported at least one protocol-
specified adverse event of any grade (2912 patients
vs. 2554 patients), but the number of patients with
life-threatening or fatal protocol-specified adverse
events was similar in the two groups (67 of 3975
[1.7 percent] and 69 of 3988 [1.7 percent], respec-
tively). Fractures were significantly more frequent
in the letrozole group than in the tamoxifen group
(5.7 percent vs. 4.0 percent, \(P<0.001\)) (Table 3),
with a significantly shorter time to a first fracture
reported within four weeks after the end of treat-
ment (\(P<0.001\)). As compared with tamoxifen, le-
trozole was associated with fewer thromboem-
bolic events (1.5 percent vs. 3.5 percent, \(P<0.001\),
a lower rate of vaginal bleeding (3.3 percent vs. 6.6
percent, \(P<0.001\)), fewer endometrial biopsies (72
of 3089 women [2.3 percent] vs. 288 of 3157 wom-
en [9.1 percent], \(P<0.001\)), and fewer invasive en-
dometrial cancers (4 of 3089 women [0.1 percent]
vs. 10 of 3157 women [0.3 percent], \(P=0.18\)).
The respective median changes in cholesterol
values from baseline to 6, 12, and 24 months were
0, 0, and −1.8 percent in the letrozole group and
−12.0, −13.5, and −14.1 percent in the tamoxi-
fen group. A total of 43.6 percent of patients in
the letrozole group and 19.2 percent of patients
in the tamoxifen group had hypercholesterol-
emia reported at least once during treatment
(grade 1 in 35.1 percent and 17.3 percent, re-
spectively). The overall incidence of adverse car-
diovascular events of grade 3, 4, or 5 was similar
in the two groups (3.7 percent in the letrozole
group and 4.2 percent in the tamoxifen group),
but more women in the letrozole group had
grade 3, 4, or 5 cardiac events (2.1 percent vs. 1.1
percent, \(P<0.001\)) (Table 3).

Table 2. Incidence of Efficacy End-Point Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Letrozole (N = 4003) number (percent)</th>
<th>Tamoxifen (N = 4007) number (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free–survival event*</td>
<td>351 (8.8)</td>
<td>428 (10.7)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>21 (0.5)</td>
<td>37 (0.9)</td>
</tr>
<tr>
<td>Contralateral-breast cancer</td>
<td>16 (0.4)</td>
<td>27 (0.7)</td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>13 (0.3)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>177 (4.4)</td>
<td>232 (5.8)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>11 (0.3)</td>
<td>19 (0.5)</td>
</tr>
<tr>
<td>Bone</td>
<td>80 (2.0)</td>
<td>99 (2.5)</td>
</tr>
<tr>
<td>Viscera</td>
<td>86 (2.1)</td>
<td>114 (2.8)</td>
</tr>
<tr>
<td>Second, nonbreast cancer</td>
<td>69 (1.7)</td>
<td>82 (2.0)</td>
</tr>
<tr>
<td>Death without prior cancer event</td>
<td>55 (1.4)</td>
<td>38 (0.9)</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>166 (4.1)</td>
<td>192 (4.8)</td>
</tr>
</tbody>
</table>
| Systemic disease-free–survival events (excluding local and contralat-
  eral-breast events)                                                 | 323 (8.1)                            | 383 (9.6)                             |

* A disease-free–survival event was defined as the first of any of the following events: any breast-cancer recurrence; a new, invasive cancer in the contra-
lateral breast; a second, nonbreast cancer; or death without a prior cancer event.
DISCUSSION

Our study confirms the positive results reported in other trials of letrozole as adjuvant treatment for hormone-receptor–positive breast cancer in postmenopausal women\(^8\)–\(^{11}\) and provides new information concerning the use of an aromatase inhibitor in this setting.\(^2\)–\(^{12}\),\(^{20}\) Particularly notable was our finding of a significant reduction in the risk of distant recurrence with letrozole, as compared with tamoxifen (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; \(P = 0.001\)). Longer follow-up is required to determine whether letrozole will continue to reduce the risk of relapse for several years after the cessation of treatment, as has been shown for tamoxifen.\(^{22}\)

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,\(^{12}\),\(^{20}\),\(^{21}\) comparing anastrozole with tamoxifen, and our trial found similar hazard ratios for similarly defined end points (occurrences of ductal carcinoma in situ, but not second, nonbreast cancers, were counted as disease-free–survival events in the ATAC trial). In subgroup analyses of the ATAC trial, the benefit of anastrozole was seen predominantly in patients who had not received adjuvant chemotherapy and those with node-negative disease, whereas in the BIG 1-98 trial, the greatest benefit of letrozole was in patients who had received chemotherapy and in those with node-positive disease. We also found that all patients with estrogen-receptor–positive tumors had a similar reduction in the risk of a disease-free–survival event associated with letrozole irrespective of their progesterone-receptor status, whereas the ATAC trial showed a beneficial effect of anastrozole mainly in patients with estrogen-receptor–positive and progesterone-receptor–negative tumors.\(^{23}\) These findings highlight the need for caution in interpreting subgroup analyses, even in large trials.

Our initial results suggest that an aromatase inhibitor should be considered in the adjuvant-treatment plan for postmenopausal women with hormone-sensitive breast cancer. The results of the BIG 1-98 trial show that tamoxifen and letrozole have different safety profiles. In patients at low risk for breast-cancer recurrence, the incidence, severity, type, and duration of side effects are relevant in selecting treatment.\(^{24}\),\(^{25}\) The safety profile of letrozole in our study is in line with findings in earlier studies.

The increased incidence of fractures among women taking letrozole in our study suggests a
need for new approaches to reduce this risk, which is associated with estrogen deprivation. The absence of an increase in the median percent change from baseline in cholesterol levels during treatment with letrozole is similar to data from the MA.17 trial of the National Cancer Institute of Canada Clinical Trials Group, which compared letrozole with a placebo. The low-grade hypercholesterolemia we found in patients given letrozole, but not tamoxifen, was also reported in a
**Table 3.** Incidence of Worst Grade of Adverse Events among Patients Included in the Safety Analysis.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Letrozole (N = 3975)</th>
<th>Tamoxifen (N = 3988)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Cerebrovascular accident or TIA</td>
<td>ND†</td>
<td>ND†</td>
<td>20</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>13†</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>51</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>4</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Other cardiovascular event</td>
<td>11</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>114</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>687</td>
<td>645</td>
<td>ND†</td>
</tr>
<tr>
<td>Night sweats</td>
<td>295</td>
<td>259</td>
<td>ND†</td>
</tr>
<tr>
<td>Fracture</td>
<td>ND†</td>
<td>148</td>
<td>77</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>467</td>
<td>263</td>
<td>74</td>
</tr>
<tr>
<td>Myalgia</td>
<td>156</td>
<td>72</td>
<td>25</td>
</tr>
</tbody>
</table>

* Adverse events were recorded during or within 28 days after study treatment. The adverse events reported in the table were recorded by the checking of specific boxes on the case-report forms, except in the case of arthralgia and myalgia, which were recorded in an “other” category and thus may have been underestimated. Grades were determined according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0), if available, and according to criteria defined by a senior IBCSG oncologist in the protocol otherwise. Fisher’s exact P values are reported for the comparison of any grade and are not adjusted for multiple comparisons. TIA denotes transient ischemic attack.

† The grade was not defined (ND) according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0); nevertheless, grade 1 thromboembolic events were reported and confirmed by investigators.

‡ This patient had a grade 1 cerebral microangiopathy.
The effect of estrogen deprivation and aromatase inhibitors on ischemic cardiac disease requires further study. The cause of the increased incidence of cardiac events of grade 3, 4, or 5 in the letrozole group, as compared with the tamoxifen group (2.1 percent vs. 1.1 percent), is unknown, but it may be due in part to a protective effect of tamoxifen on the arteries.30,31 Some32,33 but not all34,35 groups have reported that tamoxifen has a cardioprotective effect. We agree with the technology-assessment statement issued by the American Society of Clinical Oncology in 2005 that current information is insufficient to determine fully the effect of aromatase inhibitors on cardiovascular disease, especially coronary heart disease.24

In conclusion, after a median follow-up of just over two years, our results indicate that letrozole is an effective option for standard adjuvant therapy, with a relatively favorable safety profile in postmenopausal women with endocrine-responsive breast cancer.

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Dr. Thürlimann reports having received consulting fees from AstraZeneca and Pfizer and owning stock in Novartis. Dr. Mouridsen reports having received consulting fees from Novartis, AstraZeneca, and Pfizer and lecture fees from Novartis; Dr. Mauriac, lecture fees from Novartis and, in his role with the French cancer group, a grant for central coordination for the BIG 1-98 trial; Dr. Forbes, consulting and lecture fees and grant support from various nonprofit agencies in his role as head of the Australian–New Zealand Breast Cancer Trials Group; Drs. Paridaens and Smith, research grants, lecture fees, and consulting fees from AstraZeneca, Novartis, and Pfizer; Dr. Wardley, consulting and lecture fees from Novartis; and Dr. Goldhirsch, consulting and lecture fees from GlaxoSmithKline, Novartis, AstraZeneca, Roche, and Schering-Plough. No other potential conflict of interest relevant to this article was reported.

We are indebted to the patients, physicians, nurses, and data managers who participated in this clinical trial; to the BIG steering committee; to the IBCSG Data and Safety Monitoring Committee; to Novartis for funding; to the IBCSG for the design of the trial, coordination, data management, medical review, and statistical support; to the BIG groups, including the IBCSG, with participating centers from Australia and New Zealand (members of the Australia–New Zealand Breast Cancer Trials Group), Brazil, Chile (members of the Chilean Cooperative Group for Oncologic Research), Hungary, Italy, Peru, Slovenia, South Africa, Sweden (members of the West Swedish Breast Cancer Study Group), Switzerland (members of the Swiss Group for Clinical Cancer Research), and United Kingdom; the Danish Breast Cancer Cooperative Group; the French Group (Fédération Nationale des Centres de Lutte contre le Cancer); and the North Yorkshire Group; and to independent centers and groups from Argentina, Australia, Belgium, Canada, Chile, Czech Republic, Germany, Hungary, Italy, the Netherlands, New Zealand, Poland, Portugal, Russia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and Uruguay. Members of the BIG 1-98 Collaborative Group are listed in Supplementary Appendix 1.

APPENDIX

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10. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of
Rescue Angioplasty after Failed Thrombolytic Therapy for Acute Myocardial Infarction


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*The participants in the Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) trial are listed in the Appendix.

BACKGROUND
The appropriate treatment for patients in whom reperfusion fails to occur after thrombolytic therapy for acute myocardial infarction remains unclear. There are few data comparing emergency percutaneous coronary intervention (rescue PCI) with conservative care in such patients, and none comparing rescue PCI with repeated thrombolysis.

METHODS
We conducted a multicenter trial in the United Kingdom involving 427 patients with ST-segment elevation myocardial infarction in whom reperfusion failed to occur (less than 50 percent ST-segment resolution) within 90 minutes after thrombolytic treatment. The patients were randomly assigned to repeated thrombolysis (142 patients), conservative treatment (141 patients), or rescue PCI (144 patients). The primary end point was a composite of death, reinfarction, stroke, or severe heart failure within six months.

RESULTS
The rate of event-free survival among patients treated with rescue PCI was 84.6 percent, as compared with 70.1 percent among those receiving conservative therapy and 68.7 percent among those undergoing repeated thrombolysis (overall P=0.004). The adjusted hazard ratio for the occurrence of the primary end point for repeated thrombolysis versus conservative therapy was 1.09 (95 percent confidence interval, 0.71 to 1.67; P=0.69), as compared with adjusted hazard ratios of 0.43 (95 percent confidence interval, 0.26 to 0.72; P=0.001) for rescue PCI versus repeated thrombolysis and 0.47 (95 percent confidence interval, 0.28 to 0.79; P=0.004) for rescue PCI versus conservative therapy. There were no significant differences in mortality from all causes. Nonfatal bleeding, mostly at the sheath-insertion site, was more common with rescue PCI. At six months, 86.2 percent of the rescue-PCI group were free from revascularization, as compared with 77.6 percent of the conservative-therapy group and 74.4 percent of the repeated-thrombolysis group (overall P=0.05).

CONCLUSIONS
Event-free survival after failed thrombolytic therapy was significantly higher with rescue PCI than with repeated thrombolysis or conservative treatment. Rescue PCI should be considered for patients in whom reperfusion fails to occur after thrombolytic therapy.
Patients who have an open infarct-related artery after acute myocardial infarction with ST-segment elevation have better clinical outcomes than patients without an open artery.1-4 Although primary percutaneous coronary intervention (primary PCI) is a proven therapeutic approach in this setting5,6 and is used increasingly, intravenous thrombolysis remains the first-line therapy in 30 to 70 percent of cases worldwide.7,8 However, thrombolysis results in a grade 3 flow, according to the Thrombolysis in Myocardial Infarction (TIMI) classification system, in only 60 percent of patients, even with current fibrin-specific agents.9 To date, it has been unclear how best to treat the remaining patients, in whom thrombolysis has failed. Some physicians, particularly those at hospitals without interventional facilities, treat such patients conservatively.10 Others believe that a second dose of a thrombolytic agent may be beneficial.11 Many advocate emergency PCI (rescue PCI) on the basis of small trials that have suggested a benefit of this intervention.12,13 The Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) trial was undertaken to establish which of these three options achieves the best clinical outcome among patients in whom thrombolysis has failed.

METHODS

We conducted a multicenter, randomized, parallel-group trial that was approved by United Kingdom national and local ethics committees and fulfilled the conditions of the Declaration of Helsinki. The trial was funded by the British Heart Foundation; Roche Pharmaceuticals provided retéplase for repeated thrombolysis (its use was optional for physician investigators). The sponsors had no role in study design, data collection, or study analysis or in the writing of this report.

PATIENTS

Between December 1999 and March 2004, trial candidates were evaluated at 35 centers (which joined the study on a rolling basis over three years); 19 of the centers had on-site angiographic facilities. Adults 21 to 85 years of age were eligible for inclusion if they had received any licensed thrombolytic agent for myocardial infarction with ST-segment elevation within 6 hours of the onset of chest pain and if reperfusion had then failed to occur, as judged by the predetermined 90-minute electrocardiographic criterion (less than 50 percent resolution in the lead with previous maximal ST-segment elevation). The inclusion and exclusion criteria are listed in Table 1. A screening log of potential subjects was kept through November 2002 to catalogue patients who did or did not participate in the trial; however, this log was not maintained after November 2002 because of funding constraints. The trial subjects were enrolled after giving written informed consent.

RANDOMIZATION

Patients were randomly assigned by a 24-hour computer-generated random-allocation system to undergo repeated thrombolysis, conservative treatment, or rescue PCI. Patients assigned to repeated thrombolysis received a fibrin-specific thrombolytic agent (alteplase or retéplase, according to the physician’s choice) and intravenous heparin, according to standard clinical practice. Low-molecular-weight heparin was not used in the first 24 hours. Patients assigned to the conservative-therapy group received standard medical therapy for myocardial infarction without thrombolysis or PCI. To ensure a standardized group, conservative therapy included intravenous heparin for 24 hours, irrespective of the first thrombolytic agent. Heparin administration in the repeated-thrombolysis and conservative-therapy groups was titrated to an activated partial-thromboplastin time ratio of 1.5 to 2.5. Patients assigned to rescue PCI underwent coronary angiography, proceeding to angioplasty if required (i.e., if the patient had less than TIMI grade 3 flow and more than 50 percent stenosis in the infarct-related artery). Adjunctive strategies (e.g., stenting or glycoprotein IIb/IIIa receptor inhibition) were used at the discretion of the interventionist. Crossover among the three treatment groups was discouraged but was allowed if a patient had ongoing or further chest pain associated with ST-segment re-elevation or new elevation in at least two contiguous leads or had cardiogenic shock.

DATA COLLECTION

Clinical examination, electrocardiography, hematologic measurements, and biochemical tests (including measurement of cardiac biomarkers) were performed on all patients 4 hours after the initiation of the randomly assigned therapy (to account for the potential time delay to rescue PCI), at 12 and 24 hours after randomization, and at dis-
## Table 1. Criteria for Inclusion and Exclusion and Definitions of Trial End Points.

### Inclusion criteria
- Acute myocardial infarction with ST-segment elevation of more than 0.1 mV in at least two contiguous leads, excluding V1
- Aspirin and thrombolysis administered within 6 hours of onset of symptoms
- Age 21 to 85 years
- Ability to give informed consent
- At 90 minutes (±15 minutes) after the beginning of initial thrombolytic therapy, electrocardiogram shows failed thrombolytic therapy — i.e., less than 50% resolution of the ST segment in the lead showing the greatest ST-segment elevation measured from the baseline (isoelectric line) to 80 msec beyond the J point, with or without chest pain
- Rescue angioplasty, if assigned, can be performed within 12 hours of the onset of pain

### Exclusion criteria
- Probable inability to gain femoral access for intervention (e.g., severe peripheral vascular disease)
- Left bundle-branch block
- Life expectancy less than 6 months owing to noncardiac cause
- Previous inclusion in this trial at any time, or in any other clinical trial during the previous month
- Contraindication to thrombolysis (e.g., cardiopulmonary resuscitation after first thrombolytic treatment)
- Hemoglobin greater than 1.5 g/dl below normal range within previous 6 hours
- Platelet count below normal range within previous 6 hours
- For patients 75 years of age or older: systolic blood pressure above 200 mm Hg, diastolic blood pressure above 100 mm Hg, or both at any time during the current episode of pain, even if successfully reduced by therapy
- For patients less than 75 years of age: after prescription of first thrombolytic therapy, systolic blood pressure above 200 mm Hg, diastolic blood pressure above 100 mm Hg, or both on more than one occasion
- Estimated body weight less than 65 kg
- Cardiogenic shock, either in the opinion of the investigator or defined as persistent (lasting more than 30 minutes) systolic hypotension (less than 90 mm Hg) with oliguria and autonomic activation, with or without pulmonary edema despite appropriate volume replacement, and considered to be due to ventricular dysfunction rather than to any other cause
- Administration of low-molecular-weight heparin within the previous 12 hours

### Definitions of trial end points

#### Reinfarction
- During index admission: further chest pain lasting more than 30 minutes and accompanied by new electrocardiographic changes (new Q waves above 0.04 second or ST-segment elevation above 0.1 mV in two leads for more than 30 minutes), further enzyme rise, or both
- Late chest pain lasting more than 30 minutes and accompanied by new electrocardiographic changes, enzyme rise, or both

#### Cerebrovascular event
- A new focal neurologic deficit of presumed vascular cause persisting for more than 24 hours and without evidence of a nonvascular cause according to a neurologic imaging study

#### Severe heart failure
- Early heart failure: any new-onset cardiogenic shock or heart failure with pulmonary edema that is resistant to medical therapy and that occurs during the index admission and after randomization
- Late heart failure: admission to hospital for treatment of heart failure (New York Heart Association class III or IV)

#### Bleeding
- Major bleeding: decrease in hemoglobin of at least 5 g/dl during index admission, severe bleeding event (e.g., intracranial hemorrhage, hemopericardium, or hemodynamic compromise, with or without transfusion), or both
- Minor bleeding: observed bleeding during index admission, with or without a decrease in hemoglobin of at least 5 g/dl, with or without transfusion
- Blood loss with no identified site: a decrease in hemoglobin of 2 to 4.9 g/dl, or the need for transfusion, without an identified bleeding site
charge, with clinical follow-up at 1, 6, and 12 months. The components of the primary end point were continuously documented. More than 90 percent of study data were subjected to source validation according to strictly controlled criteria.

**END POINTS**
The primary end point was a composite of major adverse cardiac and cerebrovascular events at six months, including death, recurrent myocardial infarction, cerebrovascular event, and severe heart failure. The secondary end points included the components of the primary end point, as well as bleeding and revascularization. Events were adjudicated by an independent end-point committee, whose members were blinded to treatment assignment. Quality-of-life and resource-use data were collected at follow-up. Definitions of all end points are given in Table 1.

**POWER AND SAMPLE SIZE**
On the basis of the limited evidence available at the time of study design (1998), the steering committee estimated that the rate of the primary composite end point in the conservative-therapy group would approach 20 percent and hypothesized a 40 percent relative reduction in this rate in the rescue-PCI group; thus, it was calculated that 1200 patients would be required (80 percent power, \( \alpha = 0.05 \)). In December 2001, the members of the steering committee and the data and safety monitoring committee (who did not have access to the trial data) examined new published evidence suggesting that the rate of death or recurrent myocardial infarction would be 29 percent with conservative therapy, 26.5 percent with repeated thrombolysis, and 15 percent with rescue PCI. Because the rates of heart failure and cerebrovascular events were inconsistently reported in those studies, the power of our study was recalculated on the basis of assumed rates of death and recurrent myocardial infarction alone. It was determined that a sample size of 156 patients in each group would provide 80 percent power (\( \alpha = 0.05 \)) to detect the same 40 percent relative reduction in the composite end point that was previously hypothesized. It was assumed that heart failure and cerebrovascular events would be likely to increase rather than reduce such power in the final analysis.

During 2003 and 2004, enrollment in the trial began to decline. The precise reason for this decline is uncertain, because the screening log was not maintained after November 2002 (as noted above). However, other ongoing clinical trials, as well as the introduction of the new thrombolytic agent tenecteplase (and the concomitant unlicensed use of low-molecular-weight heparin), limited the number of suitable candidates for participation. Because of declining trial recruitment and a finite funding period, the steering committee terminated enrollment in the trial in March 2004.

**STATISTICAL ANALYSIS**
All analyses were performed on an intention-to-treat basis. Process times are reported as medians with interquartile ranges and compared with use of the Kruskal–Wallis test. The proportions of subjects in each of the groups who reached any end point during the six months were compared with use of either the chi-square test or Fisher’s exact test, as appropriate. Survival and event-free survival were plotted as Kaplan–Meier curves, and the log-rank test was used to compare them. Hazard ratios with 95 percent confidence intervals were calculated for all pairwise comparisons. Cox proportional-hazards regression models were used to investigate the potential influence of all baseline covariates on treatment effects. Covariates were selected for a final model by a forward variable-selection procedure. The assumption of proportional hazards was assessed both graphically, with the use of log–log survivor plots, and by adding associated time-dependent covariates to the model. There was no evidence that the assumption of proportional hazards was violated in any of the results presented here. No formal adjustment for multiple testing was undertaken, but the P values were interpreted cautiously. All statistical analyses were performed with SAS software, version 8.2 (SAS Institute).

**RESULTS**
At the termination of the trial, 435 patients had been enrolled and randomly assigned to one of the three treatment groups. Of these, six withdrew consent (one each in the groups assigned to repeated thrombolysis and rescue PCI and four in the group assigned to conservative therapy), and another two were excluded (one each in the repeated-thrombolysis and rescue-PCI groups) because they had inappropriately undergone random-
ization before giving consent, which they declined to do. The data for 427 patients are therefore presented. Of these, 142 were assigned to repeated thrombolysis, 141 to conservative therapy, and 144 to rescue PCI (Table 2).

The trial screening log, which was maintained until November 2002, included 713 patients who did not undergo randomization (as compared with 304 patients who had undergone randomization by that date). Of those who did not undergo randomization, most were excluded on the basis of clinical criteria, including delayed presentation (beyond six hours) (24 percent), advanced age (21.4 percent), and severe hypertension (13.6 percent). Only 4.2 percent were excluded on the basis of the judgment of the patient’s physician.

**BASELINE CHARACTERISTICS**

The baseline characteristics were similar in all groups (Table 2). There was no difference among the groups in the median time from the onset of pain to the first (nontrial) thrombolytic treatment ($P=0.73$). The median time from presentation until the first thrombolytic treatment (“door-to-needle time”) was 27 minutes (interquartile range, 16 to 43).

### Table 2. Baseline Characteristics of Enrolled Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Repeated Thrombolysis (N=142)</th>
<th>Conservative Therapy (N=141)</th>
<th>Rescue PCI (N=144)</th>
<th>All Patients (N=427)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>61.3 ± 10.3</td>
<td>61.0 ± 10.7</td>
<td>61.1 ± 11.9</td>
<td>61.1 ± 11.0</td>
</tr>
<tr>
<td>Range</td>
<td>40–85</td>
<td>37–85</td>
<td>34–85</td>
<td>34–85</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>114 (80.3)</td>
<td>111 (78.7)</td>
<td>113 (78.5)</td>
<td>338 (79.2)</td>
</tr>
<tr>
<td>Medical history — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>32 (22.5)</td>
<td>29 (20.6)</td>
<td>32 (22.2)</td>
<td>93 (21.8)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>23 (16.2)</td>
<td>17 (12.1)</td>
<td>14 (9.8)*</td>
<td>54 (12.7)*</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>6 (4.2)</td>
<td>4 (2.8)</td>
<td>6 (4.2)</td>
<td>16 (3.7)</td>
</tr>
<tr>
<td>Coronary-artery bypass grafting</td>
<td>7 (4.9)</td>
<td>4 (2.8)</td>
<td>7 (4.9)</td>
<td>18 (4.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (16.2)</td>
<td>16 (11.3)</td>
<td>21 (14.6)</td>
<td>60 (14.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (42.3)</td>
<td>53 (37.6)</td>
<td>47 (32.6)</td>
<td>160 (37.5)</td>
</tr>
<tr>
<td>Smoking history — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoking</td>
<td>70 (49.6)*</td>
<td>65 (46.1)</td>
<td>68 (47.2)</td>
<td>201 (47.7)*</td>
</tr>
<tr>
<td>Formerly smoked</td>
<td>41 (29.1)*</td>
<td>42 (29.8)</td>
<td>40 (27.8)</td>
<td>123 (28.9)*</td>
</tr>
<tr>
<td>Never smoked</td>
<td>30 (21.3)*</td>
<td>34 (24.1)</td>
<td>36 (25.0)</td>
<td>100 (23.5)*</td>
</tr>
<tr>
<td>Anterior infarct — no. (%)</td>
<td>54 (38.0)</td>
<td>66 (46.8)</td>
<td>61 (42.7)*</td>
<td>181 (42.5)*</td>
</tr>
<tr>
<td>First thrombolytic therapy — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reteplase</td>
<td>43 (30.3)</td>
<td>28 (19.9)</td>
<td>42 (29.2)</td>
<td>113 (26.5)</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>82 (57.7)</td>
<td>88 (62.4)</td>
<td>84 (58.3)</td>
<td>254 (59.5)</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>2 (1.4)</td>
<td>5 (3.5)</td>
<td>3 (2.1)</td>
<td>10 (2.3)</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>15 (10.6)</td>
<td>20 (14.2)</td>
<td>15 (10.4)</td>
<td>50 (11.7)</td>
</tr>
<tr>
<td>Time to first thrombolytic therapy (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>135</td>
<td>150</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>94–217</td>
<td>100–210</td>
<td>95–240</td>
<td>95–220</td>
</tr>
</tbody>
</table>

* Data were missing for one patient.
ACTUAL TREATMENT RECEIVED
Eighteen patients (4.2 percent) did not receive their randomly assigned treatment. Among the patients who were assigned to rescue PCI, 14 received conservative therapy and 2 received repeated thrombolysis; among the patients who were assigned to repeated thrombolysis, 1 received conservative therapy and 1 received rescue PCI. The results of the analysis according to the intention-to-treat principle were unchanged when the data were analyzed according to actual treatment received.

RESCUE PCI
Of the 144 patients assigned to rescue PCI, 88 (61.1 percent) were recruited from hospitals with interventional capabilities. The median transfer time for patients from hospitals without interventional capabilities was 85 minutes (interquartile range, 55 to 120). Sixteen patients in this group crossed from their assigned therapy, and 128 proceeded to angiography, 13 of whom did not require angioplasty because of patent vessels. Of the remaining 115 patients, only 9 were deemed to have had an unsuccessful rescue-PCI procedure; in 6 of these patients the artery was deemed not amenable to PCI, in one instance affecting 1 patient there was a technical failure of x-ray equipment, and in 2 patients the attempts to open the artery were unsuccessful.

Rescue PCI was commenced (i.e., the wire crossed the lesion) a median of 414 minutes after the onset of pain (interquartile range, 350 to 505). Stents were deployed in 68.5 percent of patients, and a glycoprotein IIb/IIIa receptor inhibitor (abciximab) was administered in 43.4 percent. For patients assigned to rescue PCI rather than re-

---

Table 3. End-Point Events Occurring within Six Months of Treatment.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Repeated Thrombolysis (N = 142)</th>
<th>Conservative Therapy (N = 141)</th>
<th>Rescue PCI (N = 144)</th>
<th>Overall P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end-point events (predetermined hierarchical analysis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause — no. (% of patients)</td>
<td>18 (12.7)</td>
<td>18 (12.8)</td>
<td>9 (6.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Death from cardiac causes — no. (% of patients)</td>
<td>15 (10.6)</td>
<td>14 (9.9)</td>
<td>8 (5.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Recurrent acute myocardial infarction — no. (% of patients)</td>
<td>15 (10.6)</td>
<td>12 (8.5)</td>
<td>3 (2.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebrovascular event — no. (% of patients)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>3 (2.1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Severe heart failure — no. (% of patients)</td>
<td>10 (7.0)</td>
<td>11 (7.8)</td>
<td>7 (4.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>Composite primary end point — no. (% of patients)</td>
<td>44 (31.0)</td>
<td>42 (29.8)</td>
<td>22 (15.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Secondary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed — no. of patients (no. of deaths)</td>
<td>7 (5)</td>
<td>5 (3)</td>
<td>4 (0)</td>
<td>0.65</td>
</tr>
<tr>
<td>Minor bleed — no. of patients (no. sheath-related)</td>
<td>10 (3)</td>
<td>8 (0)</td>
<td>33 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood loss with no identified site — no. of patients</td>
<td>34</td>
<td>33</td>
<td>19</td>
<td>0.12</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI or CABG — no. (% of patients)</td>
<td>33 (23.2)</td>
<td>29 (20.6)</td>
<td>19 (13.2)</td>
<td>0.08†</td>
</tr>
</tbody>
</table>

* PCI denotes percutaneous coronary intervention, and CABG coronary-artery bypass grafting. The proportions of subjects in each of the groups who reached any end point during the six months were compared by either the chi-square test or Fisher’s exact test, as appropriate.
† P = 0.05 by the log-rank test.
PCI denotes percutaneous coronary intervention, and CI confidence interval.

Failure, or Cerebrovascular Event) within Six Months.

Primary End Point (Death, Recurrent Myocardial Infarction, Severe Heart

Figure 1. Kaplan–Meier Estimates of the Cumulative Rate of the Composite Primary End Point (Death, Recurrent Myocardial Infarction, Severe Heart Failure, or Cerebrovascular Event) within Six Months.

No. of Event-free Patients
Repeate thrombolysis 110 106 105 101 99 99 96 95 93
Conservative therapy 109 104 102 99 98 97 96 95 93
Rescue PCI 129 127 124 122 120 118 117 116 115

Figure 1. Kaplan–Meier Estimates of the Cumulative Rate of the Composite Primary End Point (Death, Recurrent Myocardial Infarction, Severe Heart Failure, or Cerebrovascular Event) within Six Months.

Primary End Point

All components of the primary end point were recorded for 406 subjects (95.1 percent). Mortality status was confirmed for the remaining 21 subjects (4.9 percent): 6 each in the repeated-thrombolysis and conservative-therapy groups and 9 in the rescue PCI-group. Data on these subjects were included in the analyses as censored observations, with a median study period of 105 days (range, 5 to 177).

In the rescue-PCI group, 15.3 percent of the patients reached at least one component of the primary end point, as compared with 31.0 percent in the repeated-thrombolysis group and 29.8 percent in the conservative-therapy group (overall P=0.003) (Table 3). The rate of event-free survival (Fig. 1) was 84.6 percent in the rescue-PCI group, as compared with 70.1 percent in the conservative-therapy group and 68.7 percent in the repeated-thrombolysis group (overall P=0.004). Among patients assigned to rescue PCI, there was no significant difference in event rates between those who were transferred for intervention (16.4 percent) and those who were recruited in hospitals with on-site facilities for intervention (14.6 percent, P=0.80), and logistic-regression analysis indicated that the time to repeated PCI (up to 12 hours) had no significant effect on outcome. Although the numbers are very small, the incidence of the primary end point was much higher among those who underwent unsuccessful rescue PCI (5 of 9 patients [55.6 percent]) than among those who underwent successful rescue PCI (12 of 106 patients [11.3 percent], P=0.007).

Age and infarct site were the only baseline characteristics that were identified as predictors of the primary end point by multivariate analysis. Adjusted pairwise hazard ratios (Fig. 2) confirmed a statistically significant benefit of rescue PCI as compared with conservative therapy (hazard ratio, 0.47; 95 percent confidence interval, 0.28 to 0.79; P=0.004) and repeated thrombolysis (hazard ratio, 0.43; 95 percent confidence interval, 0.26 to 0.72; P=0.001). There was no significant difference in benefit between repeated thrombolysis and conservative therapy (hazard ratio, 1.09; 95 percent confidence interval, 0.71 to 1.67; P=0.69).

Components of the Primary End Point

There was a trend toward lower mortality at six months in the rescue-PCI group (6.2 percent) than in either the repeated-thrombolysis group (12.7 percent) or the conservative-therapy group (12.8 percent, P=0.12 for both comparisons) (Table 3). When the rescue-PCI group was compared with the two other groups combined, this difference was statistically significant (hazard ratio, 0.48; 95 percent confidence interval, 0.23 to 0.99; P=0.05). Multivariate analysis identified age and diabetes as significant predictors of death, and the adjusted hazard ratios significantly favored rescue PCI: the hazard ratio for rescue PCI as compared with repeated thrombolysis was 0.42 (95 percent confidence interval, 0.19 to 0.94; P=0.04), and the hazard ratio for rescue PCI as compared with conservative therapy was 0.42 (95 percent confidence interval, 0.19 to 0.94; P=0.04). The trial was not powered to detect a difference in mortality alone.

There were no significant differences in the rates of cerebrovascular events or severe heart failure among the three treatment groups (Table 3). However, the rate of recurrent myocardial infarction was significantly lower in the rescue-PCI group (2.1 percent) than in the repeated-thrombolysis group (10.6 percent) or the conservative-therapy group (8.5 percent); the hazard ratio for rescue PCI as compared with repeated thrombolysis was 0.47 (95 percent confidence interval, 0.28 to 0.79; P=0.004). There was no significant difference in the rates of cerebrovascular events or severe heart failure among the three treatment groups (Table 3). However, the rate of recurrent myocardial infarction was significantly lower in the rescue-PCI group (2.1 percent) than in the repeated-thrombolysis group (10.6 percent) or the conservative-therapy group (8.5 percent); the hazard ratio for rescue PCI as compared with repeated thrombolysis was 0.47 (95 percent confidence interval, 0.28 to 0.79; P=0.004).
sis was 0.23 (95 percent confidence interval, 0.09 to 0.62; \( P = 0.004 \)), and the hazard ratio for rescue PCI as compared with conservative therapy was 0.33 (95 percent confidence interval, 0.12 to 0.93; \( P = 0.04 \)).

**BLEEDING COMPLICATIONS**

Bleeding events were defined according to a modified TIMI classification (Table 1).

There were no significant differences among the groups in major bleeding events (Table 3). However, there was a tendency toward higher mortality from major bleeding episodes in the repeated-thrombolysis group (four deaths from hemopericardium and one death from intracranial hemorrhage) and the conservative-therapy group (one death from hemothorax and two deaths from intracranial hemorrhage) than in the rescue-PCI group, in which there were no deaths associated with bleeding events. Minor bleeding episodes were significantly more frequent in the rescue-PCI group (\( P < 0.001 \)); minor bleeding occurred at the access site in 28 patients, 5 of whom required blood transfusion.

Among the patients in the rescue-PCI group who had bleeding events, 69 percent had received abciximab, as compared with 43 percent of all patients in this group (\( P = 0.17 \)). There were no significant differences among the groups in the incidence of bleeding episodes characterized by a fall in hemoglobin without an identified bleeding site.

**REVASCULARIZATION**

Revascularization rates tended to be lower in the rescue-PCI group (Table 3). At six months, 86.2 percent of the patients in the rescue-PCI group were free from revascularization, as compared with 77.6 percent of those undergoing conservative therapy and 74.4 percent of those undergoing repeated thrombolysis (overall \( P = 0.05 \) by the logrank test). The unadjusted hazard ratio for revascularization was 0.50 (95 percent confidence interval, 0.29 to 0.88; \( P = 0.02 \)) for rescue PCI as compared with repeated thrombolysis and 0.58 (95 percent confidence interval, 0.33 to 1.04; \( P = 0.07 \)) for rescue PCI as compared with conservative therapy. There was no difference between the two groups not assigned to rescue PCI (hazard ratio for repeated thrombolysis as compared with conservative therapy, 1.17; 95 percent confidence interval, 0.71 to 1.92; \( P = 0.56 \)).

**DISCUSSION**

Our study compared three therapeutic options after failed thrombolytic therapy. We found that rescue PCI was superior to either conservative care or repeated thrombolysis, even though a substantial proportion of patients treated with rescue PCI were transferred from hospitals without interventional facilities, and there was a median additional time delay of 84 minutes until treatment with rescue PCI in comparison with repeated thrombolysis. A trend toward a higher frequency of fatal bleeding was noted in both the conservative-treatment group and the repeated-thrombolysis group, but given the small number of cases reported, no firm conclusions can be drawn from these data. The higher rates of nonfatal bleeding in the rescue-PCI group may be due to the use of glycoprotein IIb/IIIa receptor inhibitors.

Previous evidence supporting the use of rescue PCI is limited, and current guidelines recommend it only for certain high-risk subgroups of patients. Rescue PCI has been reported to lower the rate of recurrent myocardial infarction, reduce the incidence of early severe heart failure, and improve one-year survival. However, the sample sizes in most studies have been small; moreover, failed rescue PCI has been associated with a high incidence of adverse outcomes (approximately 30 percent), a result that could
reduce the overall benefit of the technique.\textsuperscript{21,22} The recent use of stents and glycoprotein IIb/IIIa receptor inhibitors may have improved outcomes in comparison with those in studies performed in the mid-1990s.

The findings of our study favoring the use of rescue PCI contradict those of the recent Middlesbrough Early Vascularization to Limit Infarction (MERLIN) trial,\textsuperscript{23} which found a significant reduction in revascularization rates only. There are a number of important differences between the two trials. The MERLIN trial was a locally confined study, whereas ours was a national multicenter trial. In the MERLIN trial, the first thrombolytic agent was more often streptokinase (96 percent, vs. 59 percent in our trial), and eligibility was determined on the basis of electrocardiography at 60 minutes, rather than 90. This strategy may have reduced the rates of the end points in the conservative-treatment group, since some patients treated with streptokinase probably underwent perfusion at 60 to 90 minutes (as suggested by the fact that 40 percent of the patients in the rescue-PCI group had TIMI grade 3 flow according to angiography before intervention). The MERLIN trial also showed lower rates of stenting and of glycoprotein IIb/IIIa inhibitor use, which may have contributed to a higher reinfarction rate in the rescue-PCI group. For reasons that remain unexplained, the mortality in the rescue-PCI group was unusually high in the MERLIN trial,\textsuperscript{20} as was the rate of cerebrovascular events in this group (4.6 percent). In addition, despite the absence of a group randomly assigned to repeated thrombolytic treatment, 11.7 percent of the conservatively treated patients in the MERLIN trial underwent repeated thrombolysis, further confounding the results.

The optimal approach for detecting the failure of thrombolytic therapy has been the subject of much debate.\textsuperscript{24,25} Historically, entry into studies of rescue PCI has been determined by angiographic findings,\textsuperscript{15,26} whereas in clinical practice, failure of reperfusion is generally detected by clinical, noninvasive markers. There is evidence that the ratios of biochemical markers (including creatine kinase MB fraction, troponin, and myoglobin mass) measured before and 60 minutes after the administration of thrombolytic therapy have good predictive value,\textsuperscript{27,28} with low ratios correlating with poor patency. However, differential degrees of ST-segment resolution also correlate well with TIMI flow grade\textsuperscript{29–31} and predict longer-term outcome.\textsuperscript{32} The value of ongoing pain as a sensitive marker of nonreperfusion is questionable, given its low specificity\textsuperscript{33} and the routine use of analgesia. Although certain markers (e.g., myoglobin) may be considered the most sensitive for detecting failed thrombolytic therapy, these were not widely available in the clinical setting when our trial was designed. Therefore, an ST-segment resolution of 50 percent was considered the most reliable possible entry criterion, and this cutoff was deemed likely to pick up most reperfusion failures, with a low rate of false positives for patent arteries.\textsuperscript{30,32,34}

Although the trial was terminated early, termination occurred before the investigators were unblinded to the data and was necessary, given the falling recruitment rates and the finite funding period for the study. In the absence of a full registry, we cannot exclude some element of selection bias in the population enrolled. However, all consecutive patients at each site in whom thrombolytic therapy had failed were evaluated, and the baseline characteristics as recorded in the screening log until November 2002 do not suggest such bias. The great majority of patients, according to this record, were excluded for predefined clinical reasons, with only 4.2 percent being excluded by choice of the patient’s physician.

In conclusion, the trial found that rescue PCI after failed thrombolytic treatment was associated with a statistically significant reduction in the incidence of major adverse cardiac and cerebrovascular events, as compared with either repeated thrombolysis or conservative management. These results indicate that rescue PCI, with transfer to a tertiary site if required, should be considered for patients in whom thrombolysis for myocardial infarction with ST-segment elevation fails to achieve reperfusion.

Dr. Gershlick reports having served as a consultant to and received lecture fees from Cordis, Boston Scientific, and Medtronic and being currently in receipt of research grant support from Medtronic; Dr. Baumbach, having served as a consultant to Boston Scientific; Dr. Schofield, having served as a consultant to Cordis and Guidant; and Dr. Dawkins, having served as a consultant to Eli Lilly, Boston Scientific, and Guidant, and having appeared as an expert witness for Boston Scientific. No other potential conflict of interest relevant to this article was reported.

We are indebted to Leslie Shortt for data entry, and to the nursing and medical staff of the cardiac care units and catheter laboratories at all sites.
RESOLVE ANGIOPLASTY OR REPEATED THROMBOLYSIS AFTER FAILED THROMBOLYTIC THERAPY

APPENDIX


REFERENCES


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

The Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators*

Robert J. Adams, M.D., and Donald Brambilla, Ph.D., of the STOP 2 investigative team take responsibility for the content of this article. Address reprint requests to Dr. Adams at the Department of Neurology, Medical College of Georgia, 1429 Harper St., HF 1154, Augusta, GA 30912, or at rjadams@mcg.edu.

*Principal investigators in the STOP 2 trial are listed in the Appendix.

ABSTRACT

BACKGROUND
Prophylactic transfusion prevents strokes in children with sickle cell anemia who have abnormalities on transcranial Doppler ultrasonographic examination. However, it is not known how long transfusion should be continued in these children.

METHODS
We studied children with sickle cell disease who had a high risk of stroke on the basis of a transcranial Doppler screening examination and who had received transfusions for 30 months or longer, during which time the Doppler readings became normal. The children were randomly assigned to continued transfusion or no continued transfusion. Children with severe stenotic lesions on cerebral magnetic resonance angiography were excluded. The composite primary end point was stroke or reversion to a result on Doppler examination indicative of a high risk of stroke.

RESULTS
The study was stopped after 79 children of a planned enrollment of 100 underwent randomization. Among the 41 children in the transfusion-halted group, high-risk Doppler results developed in 14 and stroke in 2 others within a mean (±SD) of 4.5±2.6 months (range, 2.1 to 10.1) of the last transfusion. Neither of these events of the composite end point occurred in the 38 children who continued to receive transfusions. The average of the last two transcranial Doppler results before transfusion was started was the only predictor of the composite end point (P=0.05).

CONCLUSIONS
Discontinuation of transfusion for the prevention of stroke in children with sickle cell disease results in a high rate of reversion to abnormal blood-flow velocities on Doppler studies and stroke. (ClinicalTrials.gov number, NCT00006182.)
STROKE CAUSES SUBSTANTIAL MORBIDITY in children with sickle cell disease. To prevent first strokes, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) used prophylactic red-cell transfusions in children who were identified by transcranial Doppler ultrasonography as being at high risk for stroke. This strategy reduced the incidence of stroke among such children from 10 percent per year to less than 1 percent per year. The STOP study led to recommendations for transcranial Doppler screening and prophylactic transfusion for children with abnormal velocities on ultrasonography. Despite the reduced risk of stroke, the potentially indefinite duration of transfusion aroused concern about adverse effects, especially iron overload.

Transfusion has been used to prevent recurrent stroke in sickle cell disease for more than 20 years. However, cessation of transfusions is associated with recurrence of stroke, and there are no clinical or laboratory indicators to guide the duration of prophylaxis. The duration of the use of transfusion for the primary prevention of stroke is also unknown. We undertook a randomized, controlled trial, the Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial, to determine whether we could limit prophylaxis by monitoring patients who had transcranial Doppler examinations after transfusions were halted and by resuming transfusions if the examination indicated a high risk of stroke.

METHODS

TRANSCRANIAL DOPPLER EXAMINATION

We conducted a study in which transcranial Doppler ultrasonographic examinations were performed by trained ultrasonographers who used similar equipment and software (2-MHz pulsed-wave Doppler, Nicolet/EME Companion or Nicolet/EME Pioneer). The Doppler studies were transmitted to central readers who were unaware of the treatment assignments. All results were recorded as the time-averaged mean of the maximum velocity in the middle cerebral or internal carotid artery and were classified as normal (all mean velocities of <170 cm per second), conditional (at least one mean velocity of 170 to 199 cm per second but none ≥200 cm per second), abnormal (at least one mean velocity of at least 200 cm per second), or inadequate (no information available on one or both middle cerebral arteries).

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) of the brain was required before patients underwent randomization, at the end of the study, and at the time of suspected neurologic events. The study protocol included axial T₁-weighted spin–echo images (repetition time, 400 to 800 msec, and echo time, 10 to 30 msec). Axial spin–echo and fluid-attenuated inversion recovery (FLAIR) T₂-weighted images, spin–echo or fast (turbo) spin–echo images with slices at a thickness of 5 mm, coronal spin–echo and FLAIR images (with the use of the same protocol as axial), and diffusion-weighted imaging (gradient strength, B 1000), with axial images in the x, y, and z planes, were performed. Magnetic resonance angiography (MRA) was standardized according to a protocol of image acquisition with the use of a three-dimensional time-of-flight technique using the smallest feasible voxel size (small field of view, 15 to 20 cm, and matrix, 256 by 256 to 256 by 512) and the shortest obtainable echo time (<5 msec) to minimize the flow-related loss of the intravascular signal. All images were reviewed for the presence, size, and location of ischemic lesions by experts who were unaware of the treatment assignment. Middle cerebral and carotid angiograms were scored as normal or as showing a stenosis that was mild (<25 percent), moderate (25 to 75 percent), or severe (>75 to <100 percent) or an occlusion.

ELIGIBILITY AND MONITORING OF PATIENTS

Figure 1 shows the design of the trial and the eligibility criteria. This trial was an extension of the previous STOP study, in which children with abnormal velocities on transcranial Doppler ultrasonographic examination were administered transfusions to prevent a first stroke. Children whose Doppler studies normalized after 30 or more months of transfusion were eligible for the present trial. In addition, children who had not participated in the previous STOP study whose condition met the criteria for eligibility and treatment were also eligible for the present study. All
TCD screening for high risk of stroke
Protocol recommended by the NHLBI

Results of one TCD examination showing a velocity of ≥220 cm/sec or results of two TCD examinations if the first showed a velocity of 200–219 cm/sec and the second showed a velocity of ≥200 cm/sec. If test results were normal, conditional, or inadequate, screening was repeated after 6 to 12 mo.

Patients meeting TCD examination criteria accepted transfusion on a clinical basis for stroke prevention (study protocol); enrolled in observation study as a “potential” candidate for randomization

Patients meeting TCD examination criteria (study protocol) but did not receive transfusion; not eligible for further study

Eligible for randomization if:
- Adequate participation in a transfusion program (≥24 transfusions in 30 mo and Hb S <30% in at least 20 of the 30 mo)
- 2 Normal TCD examinations at least 2 wk apart while receiving transfusions within 4 mo of randomization
- Age, 5–20 yr
- Consent to participate in trial

Not eligible for randomization if:
- Prior stroke
- Indication for chronic transfusion
- Contraindication for chronic transfusion
- Moderate-to-severe intracranial arterial disease on MRA

Assigned to continued transfusion

Assigned to no continued transfusion

TCD examination and clinical surveillance at least every 12 wk
- Quarterly visits
- Yearly MRI and MRA

Composite end point:
- Abnormal blood-flow velocity on TCD examination or stroke
- Offer of reinstitution of transfusion

Continuation in study

Hydroxyurea therapy or crossover to reinstitute or halt transfusion
- Patient followed but data censored
participants were required to have normal results on two consecutive transcranial Doppler studies performed at least two weeks apart while they were receiving prophylactic transfusions and within four months before randomization. The protocol was approved by the institutional review boards at the participating institutions. Written informed consent was obtained from a parent or guardian of the child in all instances, and the children's assent was obtained, when appropriate.

TRANSFUSIONS

Blood for transfusions was matched for C, D, E and Kell antigens. Chelation therapy with the use of deferoxamine was recommended if serum ferritin levels exceeded 2500 ng per milliliter, but the type of transfusion (simple, manual exchange, or automated erythrocytapheresis) and initiation of chelation treatment were at the discretion of the investigator. Patients who were randomly assigned to the transfusion-halted group could receive transfusions that were indicated to treat complications of sickle cell disease. Initiation of hydroxyurea therapy\(^\text{11}\) or regular transfusion in a patient assigned to this group was designated as a crossover and prompted censoring of data on the patient as of the date of treatment.

Information on new neurologic symptoms was solicited quarterly, and changes in medication, interim illness, and episodic transfusion were recorded. A complete blood count, reticulocyte count, quantitative hemoglobin electrophoresis, and alloantibody screening were performed before each transfusion and quarterly; and serum ferritin levels were measured at the core laboratory (at the Medical College of Georgia in Augusta). Measurements of serum alanine aminotransferase, \(\gamma\)-glutamyltransferase, lactate dehydrogenase, and bilirubin and screening for hepatitis B and C viruses were performed annually.

DEFINITION AND ADJUDICATION OF END POINTS

The primary composite end point was a stroke (cerebral infarction or intracranial hemorrhage) or reversion to abnormal velocity on transcranial Doppler ultrasonography, defined as two consecutive studies with abnormal velocities, three consecutive studies with an average velocity of 200 cm per second or more, or three consecutive inadequate studies plus evidence of severe stenosis on MRA. Suspected strokes were adjudicated by experts unaware of the treatment assignment using clinical data and all available imaging data. Stroke was defined as persistent neurologic abnormalities or transient symptoms accompanied by a new cerebral lesion appropriate to the patient’s clinical presentation.

STATISTICAL ANALYSIS

A sample size was calculated that would provide 80 percent power, with a two-tailed type I error rate of 0.05, to detect an absolute difference of 50 percentage points between the two study groups in the proportion of patients in whom a stroke occurred or who reverted to being at high risk for stroke on the basis of transcranial Doppler examination over three years. Patients were stratified at randomization according to the presence or absence of ischemic lesions on MRI; random, permuted blocks of four or six patients were used within each group as defined by MRI. Institutional balancing with a tolerance of two patients per site was imposed to maintain an approximate balance in treatment assignments at each site.\(^\text{12}\) Power calculations for the log-rank test were performed with the use of SAS software (version 8, SAS Institute),\(^\text{13}\) with the software program of Lakatos,\(^\text{14}\) for a 54-month study involving 50 patients in each group, with 60 of the patients enrolled during the first 12 months and 40 during the next 24 months; after recruitment ended, there were 18 months of follow-up. Eligible patients underwent randomization with equal probability of continuing or halting transfusion.

Baseline characteristics of the patients in the two groups were compared with the use of Student's t-tests for continuous variables and chi-square tests (for the presence or absence of lesions on MRI) or Fisher's exact test (for male or female sex) for categorical variables. Laboratory values 6 months (and in some cases, 12 months) after randomization were compared with baseline values by Student’s t-test. All reported P values are two-sided and were not adjusted for multiple testing.

Event rates were compared with the use of a log-rank test.\(^\text{15}\) Potential predictors of the primary composite end point preselected for analysis were sex, age at randomization, presence or absence of lesions on baseline MRI, transcranial Doppler readings before and after transfusion, average hemoglobin S levels before transfusion in patients receiving transfusions, and the number of transfusions received during the 30 months before
randomization. Post hoc analyses were also performed to examine whether variables that have been related to cerebral infarction were associated with stroke or reversion to abnormal velocities on Doppler examination in our study. Each of the variables (recurrent or proximate acute chest syndrome, transient ischemic attack, low total hemoglobin levels, and elevated blood pressure) was tested in a separate model.

Four interim analyses and one final analysis were planned for the composite end point, with the use of two-tailed tests, and separately for stroke alone, with the use of one-tailed tests. In both cases, the Lan and DeMets spending function that approximates an O’Brien–Fleming boundary was used.

RESULTS

The trial was stopped by the National Heart, Lung, and Blood Institute on the advice of the data safety and monitoring committee because of concern about safety at the fourth interim analysis. There were no significant differences in baseline characteristics among the patients in the two groups (Table 1). End-point events occurred in 16 patients (age at event, 8.4 to 19.7 years; median age, 11.8 years), all of whom were assigned to no continued transfusion; 14 of the events were reversion to abnormal velocities on transcranial Doppler studies, and 2 were strokes. The median time from randomization to an end-point event was 3.2 months (range, 2.1 to 10.1), and the mean (±SD) was 4.5±2.6 months. As compared with those in the continued-transfusion group, almost half the patients in the transfusion-halted group had a primary event within 10 months after randomization (Fig. 2). There was a significant (P<0.001) difference between the two groups in the number of patients having an end-point event. Eleven neurologic events were adjudicated, and of these, two were determined to be strokes. In each of the two children who had a stroke, the stroke occurred after the child had a single Doppler result showing an abnormal velocity but before a confirmatory test was performed. One child had a first abnormal result (a velocity of 210 cm per second) on day 281 after randomization and presented with a symptomatic new right-hemisphere infarction on day 295. The other child had a first Doppler result showing abnormalities on day 136 (a velocity of 231 cm per second) and had a stroke on day 144. Data on nine patients assigned to no continued transfusion who did not have a primary end-point event were censored: five of these patients resumed chronic transfusion and four started treatment with hydroxyurea. Of 38 patients assigned to continued transfusion, 5 discontinued participation in the study. Of these 38 patients, 19 received transfusions without phlebotomy, 4 received manual exchanges, and 7 received automated cytapheresis; 8 patients received transfusions by two or more methods. Hemoglobin S levels measured before transfusion were available for 988 (92 percent) of 1070 transfusions performed during the study, of the levels measured, 748 (76 percent) were less than the target level of 30 percent, 192 (19 percent) were greater than 30 percent but less than 40 percent, and 48 (5 percent) were greater than 40 percent. Nine reactions to transfusion, one of them serious and requiring hospitalization, were reported in seven patients. Lower levels of total hemoglobin and hematocrit, higher reticulocyte counts, lower indirect bilirubin values, higher levels of lactate dehydrogenase, and higher fetal and sickle hemoglobin percentages were seen at six months in the transfusion-halted group (Table 2). Mean serum lactate dehydrogenase levels were higher at 12 months in the transfusion-halted group than in the transfusion-continued group (616±240 vs. 469±164 U per liter, P=0.046). A similar trend was observed with serum indirect bilirubin values (4.6±3.3 vs. 2.3±1.6 mg per deciliter, P=0.058).

Of the variables analyzed, only the average of the two screening velocities obtained before transfusion was started was associated with the primary composite end point (P=0.05) (risk increases with velocity). With regard to variables associated with an increased risk of overt stroke in the Cooperative Study of Sickle Cell Disease, there was one transient ischemic attack in a patient assigned to no continued transfusion who later had an abnormal velocity on transcranial Doppler study and resumed transfusion. Of 41 patients assigned to no continued transfusion, 18 had one or more episodes of acute chest syndrome after transfusion was stopped. One of these 18 patients had a reversion to an abnormal velocity on transcranial Doppler study after having acute chest syndrome. Two other patients had strokes, but in both of these patients the acute chest event occurred after the end point was reached. With the history of acute chest syndrome...
during the study treated as a time-dependent binary predictor and with acute chest events that occurred after end points had been reached excluded, the occurrence of acute chest syndrome did not predict stroke or reversion to abnormalities on transcranial Doppler studies (P=0.22).

Neither baseline blood pressure nor hemoglobin levels predicted stroke or reversion to abnormal velocities on transcranial Doppler studies (P=0.51 and P=0.11, respectively).

Of 38 patients assigned to continued transfusion, 32 were still receiving transfusions at the

### Table 1. Characteristics of the Patients at Randomization.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=79)</th>
<th>Transfusion Continued (N=38)</th>
<th>Transfusion Halted (N=41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying velocity on TCD ultrasonography before transfusion — cm/sec†</td>
<td>215±13</td>
<td>215±11</td>
<td>215±15</td>
<td>0.85</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>212 (205–222)</td>
<td>213 (205–223)</td>
<td>211 (205–221)</td>
<td>0.31</td>
</tr>
<tr>
<td>Last two TCD examinations before randomization — cm/sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>141±17</td>
<td>139±16</td>
<td>143±18</td>
<td>0.31</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>146 (129–156)</td>
<td>140 (128–152)</td>
<td>149 (133–156)</td>
<td>0.07‡</td>
</tr>
<tr>
<td>Male sex — no. of patients (%)</td>
<td>33 (42)</td>
<td>20 (53)</td>
<td>13 (32)</td>
<td>0.07‡</td>
</tr>
<tr>
<td>Age — yr</td>
<td>12.2±3.2</td>
<td>12.5±3.3</td>
<td>12.0±3.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Lesions on initial MRI — no. of patients (%)</td>
<td>21 (27)</td>
<td>10 (26)</td>
<td>11 (27)</td>
<td>0.96‡</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>111±12</td>
<td>113±12</td>
<td>109±12</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic</td>
<td>60±9</td>
<td>62±8</td>
<td>59±9</td>
<td>0.24</td>
</tr>
<tr>
<td>Hemoglobin — g/dl¶</td>
<td>9.6±1</td>
<td>9.3±0.9</td>
<td>9.8±1.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Hematocrit — %¶</td>
<td>28.7±3.2</td>
<td>28.1±2.7</td>
<td>29.3±3.5</td>
<td>0.09</td>
</tr>
<tr>
<td>White-cell count — × 10⁹/mm³¶</td>
<td>11.6±3.8</td>
<td>11.5±4.1</td>
<td>11.7±3.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Reticulocyte count — %¶</td>
<td>7.8±4.5</td>
<td>8.3±4.7</td>
<td>7.3±4.3</td>
<td>0.31</td>
</tr>
<tr>
<td>Platelet count — × 10³/mm³∥</td>
<td>381±107</td>
<td>380±103</td>
<td>381±112</td>
<td>0.99</td>
</tr>
<tr>
<td>Hemoglobin S — %**</td>
<td>20±10</td>
<td>21.0±8.6</td>
<td>19±11</td>
<td>0.39</td>
</tr>
<tr>
<td>Fetal hemoglobin — %**</td>
<td>2.4±1.6</td>
<td>2.4±1.8</td>
<td>2.3±1.5</td>
<td>0.83</td>
</tr>
<tr>
<td>LDH — U/liter**</td>
<td>461±239</td>
<td>479±210</td>
<td>444±266</td>
<td>0.52</td>
</tr>
<tr>
<td>Indirect bilirubin — mg/dl††</td>
<td>2.2±1.5</td>
<td>2±1.1</td>
<td>2.4±1.9</td>
<td>0.24</td>
</tr>
<tr>
<td>Ferritin — ng/ml**</td>
<td>3136±1607</td>
<td>3274±1718</td>
<td>3005±1504</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. P values were calculated by Student’s t-test, except where indicated otherwise. TCD denotes transcranial Doppler, MRI magnetic resonance imaging, and LDH lactate dehydrogenase.
† The value is the average of two qualifying TCD examinations performed before transfusion that showed abnormal velocities or one TCD examination if the velocity was more than 220 cm per second (for new patients entering the STOP 2 trial).
‡ The value was calculated by Fisher’s exact test.
§ The value was calculated by the chi-square test.
¶ Two patients in the transfusion-halted group were excluded, one because no baseline laboratory values were available, and the other because the blood sample was too old to be processed.
∥ Four patients were excluded, one from the continued-transfusion group because the blood sample was clotted and could not be processed, and three from the transfusion-halted group (one because no baseline blood sample was available, one because the blood sample was too old to be processed, and one because the blood sample was clotted).
** Baseline laboratory values were not available for one patient in the transfusion-halted group.
†† Two patients were excluded, one in the transfusion-halted group because baseline laboratory values were not available and the other in the continued-transfusion group because of missing data. To convert values for bilirubin to micromoles per liter, multiply by 17.1.
end of the study, 5 stopped transfusions, and 1 died of complications of acute chest syndrome. Of 41 patients assigned to no continued transfusion, 9 recommenced transfusion or started hydroxyurea treatment, and 16 were being followed without treatment or end-point events at the end of the study (8 of the 16 for more than 25 months).

At the end of the trial, 35 patients (93 percent) assigned to continued transfusion and 31 (76 percent) assigned to no continued transfusion were receiving chelation. No cases of hepatitis C were identified among the 68 patients who had serologic testing at the end of the study. One new case of alloimmunization in a patient in the continued-transfusion group was identified (anti-Kpa was detected on day 39 after randomization). At baseline, ferritin levels were 3274±1718 ng per deciliter among those assigned to continued transfusion, as compared with 3005±1504 ng per deciliter among those assigned to no continued transfusion (P=0.46). However, after 12 months, the mean levels of ferritin were 3562±1536 ng per milliliter (25 patients) and 1832±916 ng per milliliter (11 patients), respectively (P=0.002).

**Discussion**

Although chronic transfusion is effective in preventing stroke in sickle cell disease, this therapy carries immediate and cumulative risks, especially with regard to iron loading.18 Our goal was to determine whether we could safely discontinue protective transfusion in selected patients by monitoring them with transcranial Doppler ultrasonography and reinstituting transfusion if there were abnormal velocities on the Doppler study. We investigated this in children who we thought had a low risk of stroke: all originally had abnormal velocities on Doppler studies that normalized during a trial of prophylactic transfusion, and there was no evidence in these patients of clinically significant intracranial arterial stenosis on MRA. However, the difference in the number of primary end-point events exceeded the stopping boundary, and despite frequent Doppler studies, stroke was not prevented in two children.

How transfusion prevents stroke in sickle cell disease is unknown. Although there is a proportional reduction in flow velocity with increased levels of total hemoglobin,19 the increase in red-cell mass may not be the only beneficial effect. Transfusion may reduce red-cell adhesion20 to endothelium, thereby decreasing vascular injury by sickle red cells. Reduction of intravascular hemolysis and the resulting free hemoglobin, which consumes nitric oxide,21 may increase the capacity for cerebral vasodilatation in response to ischemic stress. In the STOP 2 study, plasma free hemoglobin was not measured, but lactate dehydrogenase, which has been used as a surrogate marker for hemolysis in sickle cell disease,22 was measured at baseline and yearly. There were no significant differences between the continued-transfusion group and the transfusion-halted group in baseline levels of lactate dehydrogenase (479±210 U per liter and 444±266 U per liter, respectively). At one year the levels of lactate dehydrogenase had increased from baseline in the transfusion-halted group (616±240 U per liter) but not in the continued-transfusion group (469±164 U per liter; P=0.046 by Student’s t-test for the difference between the two groups at one year). This finding suggests that one of the benefits of regular transfusion may be to reduce intravascular hemolysis, but further direct studies measuring plasma free hemoglobin23 in relation to other effects of transfusion, such as reduction of hemo-
globin S–containing red cells and increased total hemoglobin, are needed.

The risk of stopping transfusion that is demonstrated in our study highlights the need for alternative therapies to prevent stroke or better ways to manage iron overload. Reduced transfusion intensity, which allows the target value for the percentage of hemoglobin S to rise from 30 percent to 50 or 60 percent after some years of intensive transfusion, has been tried after sickle cell–related stroke without an apparent increase in the risk of stroke, but randomized trials comparing different intensities of transfusion have not been reported. A regimen of phlebotomy and hydroxyurea was substituted for chronic transfusion for secondary prevention of stroke with encouraging results, although a randomized trial is still needed. Transcranial Doppler screening has been used since 1992 by Bernaudin et al. Children with abnormal blood-flow velocities on Doppler ultrasonography are offered either hematopoietic stem-cell transplantation or transfusion. Among those electing transfusion, if the Doppler results normalize within three months after transfusion is started, and if severely stenotic arterial lesions are absent, the children are switched from transfusion to hydroxyurea therapy and followed with transcranial Doppler

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**Table 2. Laboratory Values Six Months after Randomization.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 54)</th>
<th>Transfusion Continued (N = 31)</th>
<th>Transfusion Halted (N = 23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.6±1.2</td>
<td>9.4±0.9†</td>
<td>7.7±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>8.6 (7.9–9.5)</td>
<td>9.4 (8.8–10.1)</td>
<td>7.9 (6.9–8.4)</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.3±3.9</td>
<td>27.8±2.5†</td>
<td>22.0±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>25.7 (22.9–28.4)</td>
<td>28.0 (26.3–29.3)</td>
<td>22.1 (19.2–24.4)</td>
<td></td>
</tr>
<tr>
<td>White-cell count (× 10³/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.1±3.6</td>
<td>11.9±3.6†</td>
<td>12.4±3.7</td>
<td>0.62</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>12.1 (10.4–14.5)</td>
<td>11.9 (8.9–14.9)</td>
<td>12.1 (10.7–13.8)</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.5±5.3</td>
<td>8.9±3.3†</td>
<td>14.8±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>10.2 (8.3–14.9)</td>
<td>8.8 (6.6–11.2)</td>
<td>15.4 (10.2–18.6)</td>
<td></td>
</tr>
<tr>
<td>Platelet count (× 10³/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>410.5±108</td>
<td>394.6±92.7†</td>
<td>431.3±124.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>416 (337–482)</td>
<td>424.5 (320–454)</td>
<td>398 (339–513)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin S (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49.1±30.3</td>
<td>25.4±10.9</td>
<td>81.0±13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>37.4 (25.3–85.4)</td>
<td>26.1 (19.6–31.4)</td>
<td>85.9 (74–91.5)</td>
<td></td>
</tr>
<tr>
<td>Fetal hemoglobin (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.5±3.9</td>
<td>2.6±2.1</td>
<td>7.0±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>3.4 (1.5–6)</td>
<td>1.5 (1.0–3.5)</td>
<td>5.8 (3.5–10.2)</td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3150±1843</td>
<td>3555±2043</td>
<td>2604±1394</td>
<td>0.06</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>3008 (1624–3974)</td>
<td>3254 (1996–5861)</td>
<td>2188 (1460–3309)</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. P values were calculated with the use of Student’s t-test. Only patients who completed six months of follow-up without having an end-point event and without deviating from the assigned treatment were included in the analysis.
† One patient in the group was excluded because a complete blood count and reticulocyte count were not available.
tests. This approach should be tested in a randomized, controlled trial.

In the STOP 2 study, eight patients (20 percent of those assigned to no continued transfusion) who were observed for more than 25 months without prophylactic transfusion therapy had neither a stroke nor reversion to abnormal velocities on Doppler studies. Unfortunately, there is no way to identify such patients prospectively. In the 209 patients who underwent randomization in the STOP and STOP 2 studies, there were 20 strokes (18 in STOP and 2 in STOP 2). The last transcranial Doppler examination before the stroke showed abnormal velocities in all cases, confirming that abnormal velocities on transcranial Doppler ultrasonography are a good indicator of the risk of stroke, both before transfusion is initiated and after it is stopped. These results suggest that if stroke is to be prevented after transfusion is stopped, transcranial Doppler examinations must be performed at frequent intervals and transfusion resumed expeditiously. Although morbidity and mortality from stem-cell transplantation are a concern, limited experience suggests that cerebrovascular disease does not progress after stem-cell transplantation. Given the transfusion dependence demonstrated in the STOP 2 study, and given the problems associated with long-term transfusion to prevent stroke, stem-cell transplantation should be considered as an option for primary stroke prevention.

Supported by grants (U01 HL 052193 and U01 HL 052016) from the National Heart, Lung, and Blood Institute.

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

The article is dedicated to the memory of Katie Allen, R.N., Charles Pegelow, M.D., and David Ode, M.D.

We are indebted to the patients and their families for their contribution to this research.

APPENDIX

The STOP 2 team of principal investigators is listed according to site (in descending order of the number of patients who underwent randomization): M. Abboud, J. Barredo, C. Brown, Medical University of South Carolina, Charleston; O. Alvarez, C. Pegelow, University of Miami School of Medicine, Miami; V. McKie, K. McKie, Medical College of Georgia, Augusta; E. Vichinsky, K. Quirolo, Children’s Hospital of Oakland, Oakland, Calif.; C. Driscoll, Children’s National Medical Center, Washington, D.C.; C. Daeschner, East Carolina University, Greenville, N.C.; S. Piomelli, M. Lee, Columbia University, New York; R. Iyer, University of Mississippi Medical Center, Jackson; P. Lane, B. Gee, B. Files, T. Adamkiewicz, C. Davis, Emory University School of Medicine, Grady Health System, Morehouse School of Medicine, and Children’s Healthcare of Atlanta, Atlanta; M. Kirby, Hospital for Sick Children, Toronto; N. Olivier, University Health Network, Toronto; B. Berman, A. Villella, Rainbow Babies and Children's Hospital, Cleveland; G. Woods, Children’s Mercy Hospital, Kansas City, Mo.; W. Wang, St. Jude Children’s Research Hospital, Memphis, Tenn.; J. Kwiatkowski, The Children’s Hospital of Philadelphia, Philadelphia; Baltimore–Washington Sickle Cell Research Consortium (J.F. Casella, Johns Hopkins University School of Medicine, Baltimore; J. Wiley, Sinai Hospital of Baltimore, Baltimore; N. Grossman, University of Maryland, Baltimore; A. Shad, Georgetown University, Washington, D.C.); L. Hilliard, University of Alabama at Birmingham, Birmingham; A. Provvisor, Columbus Regional–The Medical Center, Columbus, Ga.; S.T. Miller, SUNY Downstate Medical Center, Kings County Hospital Center, Brooklyn, N.Y.; T. Coates, University of Southern California, Los Angeles; R. Warrier, D. Ode, Louisiana State University, New Orleans; C. Scher, Tulane University Medical School, New Orleans; K. Kalinyak, Children’s Hospital Medical Center, Cincinnati; National Heart, Lung, and Blood Institute (NHLBI): D.R. Bonds (program officer), R.B. Moore, M. Mathis, L. Barbosa, M. Wacławski.

REFERENCES


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Trial Registration at ClinicalTrials.gov between May and October 2005

Deborah A. Zarin, M.D., Tony Tse, Ph.D., and Nicholas C. Ide, M.S.

ABSTRACT

BACKGROUND
Clinical trial registration allows interested parties to obtain information about ongoing and completed trials, but there are few data indicating the quality of the information provided during the registration process. We used information in the publicly available ClinicalTrials.gov database to describe patterns of trial registration before and after the implementation by journal editors of a new policy requiring registration as a prerequisite for publication.

METHODS
We reviewed ClinicalTrials.gov records to determine patterns of completion of the “Intervention Name” and “Primary Outcome Measure” data fields for trials registered on May 20 and October 11, 2005, and for trials registered during the interval between these two dates, inclusively.

RESULTS
During the interval studied, the number of registrations in ClinicalTrials.gov increased by 73 percent from 13,153 to 22,714. The percentage of interventional trials registered by industry with nonspecific Intervention Name entries (attributable to four drug companies) decreased from 10 percent to 2 percent; all other industry and nonindustry records contained specific entries in this field. Of the 2670 studies registered by industry between the two dates, 76 percent provided information in the Primary Outcome Measure field, although these entries varied markedly in their degree of specificity. In the remaining 24 percent of the records, this field was blank.

CONCLUSIONS
During the summer of 2005, there were large increases in the number of clinical trial registrations. Overall, the data contained in records were more complete in October than they were in May, but there still is room for substantial improvement.
Concern about previously undisclosed safety problems with drugs such as paroxetine (Paxil, GlaxoSmithKline) and rofecoxib (Vioxx, Merck) has increased the public’s desire for more complete information about clinical research studies.1-2 The provision of basic information about clinical trial protocols in a publicly accessible registry and the public identification of all trials, whether or not their results are subsequently published, have been advocated as ways to address this issue.3-6 Numerous groups have called for comprehensive registration by issuing statements or convening meetings to discuss policy and implementation details.7-15

In the United States, the Food and Drug Administration (FDA) Modernization Act, section 113 (FDAMA 113), mandates the registration of all private and public trials that test effectiveness for “serious or life-threatening” conditions submitted to the FDA under investigational-new-drug applications (IND).16 A Web-based registry, ClinicalTrials.gov, was established in 2000 by the National Library of Medicine on behalf of the National Institutes of Health as a result of this law.17-18 Although FDAMA 113 mandates the registration of certain data elements, ClinicalTrials.gov also includes a broad set of optional data elements. In addition, ClinicalTrials.gov permits the registration of any clinical trial, regardless of its IND status, the type of intervention (e.g., surgical procedure, device, or drug), the medical condition, or the country of origin. As of late October 2005, the registry contained more than 23,000 trials.

We examined the completeness and utility of the information contained in trial-registration records in ClinicalTrials.gov from May 20 through October 11, 2005. This period includes time both before and after September 13, 2005, the date of implementation of the International Committee of Medical Journal Editors (ICMJE) policy requiring the registration of clinical trials as a prerequisite for consideration for publication.7,8

Methods

The Registry

Sponsors, principal investigators, or other persons or organizations with primary responsibility for a given clinical trial (called “data providers”) can register with ClinicalTrials.gov through a Web-based system (http://prsinfo.ClinicalTrials.gov).19 In some instances, “intermediary trial registries,” such as that of the National Cancer Institute (www.cancer.gov), provide trial data. The database uses both open-ended responses and menu-based options, and terms from the National Library of Medicine Unified Medical Language System20,21 are used to facilitate subsequent information retrieval. Trials with the same protocol that are conducted at multiple sites are considered one trial in the registry. The complete entry in the registry for a given trial is referred to as a record in the database.

ClinicalTrials.gov includes both mandatory and optional data elements. Trials cannot be registered without the completion of all mandatory data elements, which include both FDAMA 113 and registry-imposed requirements. In addition, the ICMJE requires completion of some of the optional data elements. Members of the National Library of Medicine staff manage the quality of information in the registry by rejecting records that do not have all required fields completed, reviewing entries for appropriate content and internal consistency, ensuring that links are active and relevant, checking contact information for recruiting studies, and confirming that approval from an institutional review board has been obtained. In addition, sponsoring organizations must elec-
tronically sign off on all entries (and subsequent revisions) before they are made available on the Web site.

STUDY 1: ALL INTERVENTIONAL TRIALS
We described the numbers and types of trials registered in ClinicalTrials.gov. Because records in ClinicalTrials.gov can be modified at any time by data providers to keep the information current, this study was conducted with data that were available to the public on May 20, 2005 (before the September 13, 2005, implementation of the ICMJE policy on trial registration) and on October 11, 2005 (four weeks after implementation of the policy). We also reviewed data from trials registered between these two dates, inclusively, which we refer to as the interval sample (Fig. 1A). Searches of ClinicalTrials.gov were accomplished with the use of a National Library of Medicine reporting tool, although they could be replicated with the use of the public search function in combination with individual inspection of those data.

STUDY 2: “INTERVENTION NAME” FIELD
We reviewed ClinicalTrials.gov records to determine patterns of completion for the ICMJE-required data element termed “Intervention Name.” FDAMA 113 mandates completion of this field, although it does not specify how informative the entry must be, thereby limiting our ability to enforce the use of specific drug names.

We reviewed Intervention Name fields to see whether the information provided gave clinically meaningful insight into the specific treatment that was being tested. For example, a preliminary review of records showed that nonspecific terms such as “investigational drug,” rather than the name of the drug under study, were occasionally used. We limited our review of this field to interventional trials of drugs or vaccines (Fig. 1B). Records were considered acceptable if they specified at least one drug name or unique company identifying serial number. We did not evaluate the completeness of information provided about comparison interventions in a study. For example, a record that lists in the Intervention Name field “acetylsalicylic acid compared with active comparator” would have been considered acceptable for the purpose of this study, even though the information contained was not as clinically meaningful as it would have been if specific names for both drugs had been given.

STUDY 3: “PRIMARY OUTCOME MEASURE” FIELD
We reviewed ClinicalTrials.gov records to determine patterns of completion for the field termed “Primary Outcome Measure.” This field requests information about the outcome measure used to determine the statistical power of the study. It reflects the primary effect that the intervention is designed to modify. The definition of this data element in the registry states that it should include the measure used and the time of measurement relative to the start of the intervention, such as “death at 180 days after the start of treatment.”

This field has been available in ClinicalTrials.gov only since October 2004, and completion was initially mandatory for most nonindustry data providers, whereas it has always been optional for industry providers. (Before June 2005, completion of the field was mandatory for all non-IND studies, which accounted for 79 percent of the nonindustry studies and 4 percent of the industry studies. Completion of the field is now optional for all data providers.) To examine how the field is used by data providers in the absence of enforcement by ClinicalTrials.gov, we limited our analysis to industry-registered interventional trials registered between May 20 and October 11, 2005 (Fig. 1C).

We first tabulated the number of trials with and without any entry in the Primary Outcome Measure field. We stratified data for the top 20 pharmaceutical companies, ranked according to volume of U.S. drug sales. We examined the relationship between completion of this field and the phase of the study. We also assessed the quality of the entries in this field by noting whether or not they specified a measure and a time point. This subjective assessment was made (by one of us) on a sample of the records for phase 2, 3, and 4 drug studies registered by the top 10 drug companies during the interval between May 20 and October 11.

STATISTICAL ANALYSIS
We report primarily descriptive statistics. We used a chi-square test to examine the relationship between completion of the Primary Outcome Measure field and phase of study.

RESULTS
STUDY 1: ALL INTERVENTIONAL TRIALS
On May 20, 2005, there were 13,153 records in ClinicalTrials.gov; the number had increased to
22,714 as of October 11, 2005. This increase was largely attributable to a spike in registrations during the period immediately before and after September 13, 2005 (Fig. 2). Table 1 contains data on the number of trials registered according to key trial characteristics. There were increases in registered trials from all categories of data providers. The sharpest rise was in the category comprising universities, foundations, and other nongovernmental, nonindustry providers. The number of trials registered by commercial sponsors more than doubled, including an increase in the number of IND studies, from 2010 to 3516, and an increase in the number of non-IND studies, from 77 to 1348. Overall, the number of data providers increased from 667 to 1969 during this time. Among commercial sponsors, the number of companies registering trials rose from 328 to 575; among the latter were all of the top 20 pharmaceutical companies (according to volume of sales in the United States in 2005)\(^23\) and 14 of the top 20 medical-device companies (according to estimated volume of global sales in 2004).\(^24\)

We examined the interval sample to determine whether there was a change in registration behavior coincident with the implementation of the ICMJE policy. This sample included 2670 interventional studies registered by industry: 6 percent were phase 1, 28 percent phase 2, 47 percent phase 3, and 19 percent phase 4 trials. FDAMA 113 requires commercial sponsors to register only trials performed under an IND application. However, among the trials added to the database during the interval examined, 45 percent were non-IND studies, as compared with only 4 percent on May 20, 2005. As of October 11, 2005, 59 percent of the 1167 data providers from universities, foundations, and other nongovernmental, nonindustry organizations were based outside the United States. During the interval period, 52 percent of the 5307 trials registered by these 1167 data providers were conducted outside the United States, as compared with 21 percent of the 249 trials registered by this sort of provider before May 20, 2005.

**STUDY 2: INTERVENTION NAME FIELD**

The Intervention Name field was completed with a specific entry in 100 percent of the nonindustry records at both time points. The percentage of industry records with a nonspecific entry dropped from 10 percent to 2 percent during the study period (Table 2). All the nonspecific entries at both

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**Figure 2. New Trials Registered in ClinicalTrials.gov, According to Week.**

The figure shows the number of new registrations per week (beginning on the date indicated) from mid-May through early October 2005. The “Industry” category includes all commercial data providers; the “Federal” category includes the National Institutes of Health and other U.S. federal data providers; and the “University” category includes universities, foundations, and other providers.
time points were attributable to four drug companies: Merck, GlaxoSmithKline, Pfizer, and Lilly. On May 20, 2005, the percentage of trials with nonspecific entries in this field varied from 91 percent (Merck) to 3 percent (Lilly). Between May 20 and October 11, 2005, only two companies, GlaxoSmithKline and Pfizer, created new records with nonspecific intervention names, in 1 percent and 6 percent of their entries, respectively. Merck, GlaxoSmithKline, and Pfizer also added specific information to previously vague entries during the study period; Merck made the most dramatic changes, by reducing their number of nonspecific entries from 91 percent on May 20 to less than 1 percent on October 11 (Table 2). However, on October 11, there were noninformative entries in 21 percent of GlaxoSmithKline records and 11 percent of Pfizer records.

**STUDY 3: PRIMARY OUTCOME MEASURE FIELD**

Use of the Primary Outcome Measure field was assessed in the interval sample only. Information had been entered in this field in 2033 of 2670 records registered by industry (76 percent) during the study interval. Seventy percent of the records (range, 0 percent to 100 percent) from the top 20 drug companies included information in this field (Table 3). The rates of completion of this field were 77 percent for phase 1 studies, 79 percent for phase 2 studies, 76 percent for phase 3 studies, and 65 percent for phase 4 studies ($\chi^2 = 26.21$, with 3 df; $P < 0.001$).

The clinical value of the information provided in the Primary Outcome Measure field varied. Table 4 shows five categories of quality based on the specificity of the information about the primary outcome measure and the inclusion of information about the time it was measured. The 657 phase 2, 3, or 4 records from the top 10 drug companies that had entries in this field were reviewed and assigned to one of these categories. Table 4 shows that 17 percent of the entries were vague, whereas the others had varying degrees of useful information.

**DISCUSSION**

Our findings support the conclusion that ICMJE policy has had an effect on trial-registration practices. Among commercial sponsors, there was an increase in the registration of both IND and non-IND studies. Nonindustry data providers also dramatically changed their registration behavior around the time of the ICMJE deadline. The 73 percent increase in trials registered during this time was associated with a 195 percent increase in the number of data providers from around the world. Since these new providers seem to have registered in order to comply with ICMJE policy, it is likely that they will continue to register trials.

Examination of data-element usage in ClinicalTrials.gov suggests that the act of registration alone is not a good indicator of adherence to registration policies. When trial sponsors have the option of providing information of marginal clinical value in a particular data field, our findings show that some companies provide useful information and others do not. This heterogeneous behavior may indicate varying degrees of comfort with different levels of disclosure. For example, among data elements not examined in this trial, there has been a learning curve, with some companies being slower than others to provide mandatory items such as the name of the sponsor and the location of the trial.

Completion of the Intervention Name field is mandatory for all trials in ClinicalTrials.gov, but the use of specific terms has not been enforced. We determined that three industry data provid-
### Table 2. Number and Disposition of Records from Industry Providers for Interventional Trials with Nonspecific Entries in the “Intervention Name” Field.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Records with Nonspecific Entries no./total no. of trials</td>
<td>Records Corrected with Addition of Company Serial Number no.</td>
<td>Records Corrected with Addition of Drug Name no.</td>
</tr>
<tr>
<td>Merck</td>
<td>120/132</td>
<td>25</td>
<td>94</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>53/104</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pfizer</td>
<td>22/75</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lilly</td>
<td>3/96</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other industry</td>
<td>0/1619</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>198/2026</td>
<td>29</td>
<td>100</td>
</tr>
</tbody>
</table>

* Specific providers are listed in descending order of the number of nonspecific records as of May 20, 2005.

### Table 3. Use of the “Primary Outcome Measure” Field by 20 Drug Companies from May 20 through October 11, 2005.

<table>
<thead>
<tr>
<th>Rank According to U.S. Drug Sales*</th>
<th>Company</th>
<th>No. of Records with Primary Outcome Measure</th>
<th>Total No. of Records</th>
<th>Percentage of Records with Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pfizer</td>
<td>221</td>
<td>224</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>GlaxoSmithKline</td>
<td>63</td>
<td>66</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Johnson &amp; Johnson</td>
<td>57</td>
<td>63</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Merck</td>
<td>9</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>AstraZeneca</td>
<td>51</td>
<td>52</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>Novartis</td>
<td>8</td>
<td>239</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Amgen</td>
<td>65</td>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>Sanofi–Aventis</td>
<td>19</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Bristol-Myers Squibb</td>
<td>53</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>Lilly</td>
<td>121</td>
<td>136</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>Wyeth</td>
<td>53</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>Abbott</td>
<td>19</td>
<td>34</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>Hoffmann–La Roche</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>TAP Pharmaceutical</td>
<td>22</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>Boehringer Ingelheim</td>
<td>48</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>16</td>
<td>Teva (Teva Neuroscience)</td>
<td>14</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>17</td>
<td>Schering-Plough</td>
<td>1</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>Forest Laboratories</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>19</td>
<td>Eisai</td>
<td>31</td>
<td>35</td>
<td>89</td>
</tr>
<tr>
<td>20</td>
<td>Watson</td>
<td>15</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>Total for the 20 companies</td>
<td>871</td>
<td>1247</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

* Data on rank according to volume of U.S. sales are from IMS Health.²¹
ers — Merck, GlaxoSmithKline, and Pfizer — used a nonspecific term, such as “investigational drug,” between 29 percent and 91 percent of the time in trials registered as of May 20, 2005. These three companies are ranked in the top five according to volume of U.S. drug sales. Lilly used nonspecific intervention names in 3 of its 96 entries (3 percent). In contrast, other data providers, including 571 other industry providers, entered specific information (either a name or a serial number) in this field in all their records. Between May 20 and October 11, only two drug companies, GlaxoSmithKline and Pfizer, used a nonspecific term in this field, and then only rarely. In addition, many of the previously identified nonspecific records were corrected with the addition of drug names or serial numbers.

Our assessment of the quality of information in the Intervention Name field is limited by our methods. Our search revealed only records that had an easily identified term, such as “investigational drug,” in lieu of a drug name. As a result, entries such as “tyrosine kinase inhibitor” or “antibiotic” were not captured in our search for nonspecific terms. In addition, we were not able to evaluate the degree to which interventions in all groups in a study were delineated. Such information is critical to the full description of a clinical trial. Structures for collecting and monitoring the quality of this information need to be developed.

The Primary Outcome Measure field has been available since October 1, 2004. Before May 20, 2005, this field was commonly left blank by industry and other data providers. Since then, 76 percent of industry records have included an entry in this field, although the percentages vary widely according to company (Table 3). In general, information in this field is more likely to be omitted for phase 4 trials. In addition, the quality and completeness of the entries vary with respect to standard attributes of outcome measures. The attributes presented in Table 4 are consistent with those identified in global standards, such as the Tripartite Harmonised ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline E32 and the ICMJE statement.8 Although we examined only industry records, the use of this field by all data providers will need to be monitored and discussed. It is not clear how ClinicalTrials.gov can best provide information about outcome measures to the full range of interested parties, including patients, clinicians, researchers, and policymakers. In the meantime, more structured guidelines for listing outcome measures might enhance the utility of data in ClinicalTrials.gov and other registries.

Evaluation of compliance with the legal mandate for trial registration, FDAMA 113, shows improving but imperfect compliance on the part of industry.25 Although we cannot judge the degree of compliance with ICMJE policy, which is not

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Table 4. Attributes of Entries in “Primary Outcome Measure” Field.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Frequency (N = 657)*</th>
<th>Examples from ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vague</td>
<td>17%</td>
<td>Clinical response, Tolerability</td>
</tr>
<tr>
<td>Domain without specific measure</td>
<td>19%</td>
<td>Glucose regulation, Severity of symptoms of schizophrenia</td>
</tr>
<tr>
<td>Specific measure without time frame</td>
<td>23%</td>
<td>Intravenous glucose-tolerance test, Structured clinical interview — positive and negative syndrome scale, No. of hospitalizations</td>
</tr>
<tr>
<td>Time frame without specific measure</td>
<td>10%</td>
<td>Tumor response at 3 mo, Freedom from progression at 2 yr, Improvement in glucose control over 16-wk period</td>
</tr>
<tr>
<td>Specific measure and time frame</td>
<td>31%</td>
<td>Change in glycosylated hemoglobin from baseline to 6 mo, Mortality from any cause at 30 days</td>
</tr>
</tbody>
</table>

* Frequencies are based on a review of 657 records from the top 10 drug companies, ranked according to data from IMS Health on the volume of U.S. sales.23 Phase 2, 3, and 4 trials were included.
legally binding, without knowing the number of clinical trials overall, our data indicate large increases in trial registration from all sectors. Some commercial organizations and other stakeholders note that the mandatory registration of exploratory trials (roughly, phase 1 and 2 trials) and the prospective disclosure of certain data elements, including intervention name and primary outcome measure, raise critical proprietary issues. These concerns may explain some of the variations in registration practices that are evident in our data.

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

We are indebted to Annice M. Bergeris for assistance with sample selection, data analysis, and comments on drafts of the manuscript; to In Hye Cho for assistance with data analysis; and to Drs. Donald A.B. Lindberg and Stephen G. Pauker for review of drafts of the manuscript.

REFERENCES

Trial Registration at ClinicalTrials.gov between May and October 2005

Deborah A. Zarin, M.D., Tony Tse, Ph.D., and Nicholas C. Ide, M.S.

ABSTRACT

BACKGROUND
Clinical trial registration allows interested parties to obtain information about ongoing and completed trials, but there are few data indicating the quality of the information provided during the registration process. We used information in the publicly available ClinicalTrials.gov database to describe patterns of trial registration before and after the implementation by journal editors of a new policy requiring registration as a prerequisite for publication.

METHODS
We reviewed ClinicalTrials.gov records to determine patterns of completion of the “Intervention Name” and “Primary Outcome Measure” data fields for trials registered on May 20 and October 11, 2005, and for trials registered during the interval between these two dates, inclusively.

RESULTS
During the interval studied, the number of registrations in ClinicalTrials.gov increased by 73 percent from 13,153 to 22,714. The percentage of interventional trials registered by industry with nonspecific Intervention Name entries (attributable to four drug companies) decreased from 10 percent to 2 percent; all other industry and nonindustry records contained specific entries in this field. Of the 2670 studies registered by industry between the two dates, 76 percent provided information in the Primary Outcome Measure field, although these entries varied markedly in their degree of specificity. In the remaining 24 percent of the records, this field was blank.

CONCLUSIONS
During the summer of 2005, there were large increases in the number of clinical trial registrations. Overall, the data contained in records were more complete in October than they were in May, but there still is room for substantial improvement.
Concern about previously undisclosed safety problems with drugs such as paroxetine (Paxil, GlaxoSmithKline) and rofecoxib (Vioxx, Merck) has increased the public’s desire for more complete information about clinical research studies.1-2 The provision of basic information about clinical trial protocols in a publicly accessible registry and the public identification of all trials, whether or not their results are subsequently published, have been advocated as ways to address this issue.3-6 Numerous groups have called for comprehensive registration by issuing statements or convening meetings to discuss policy and implementation details.7-15

In the United States, the Food and Drug Administration (FDA) Modernization Act, section 113 (FDAMA 113), mandates the registration of all private and public trials that test effectiveness for “serious or life-threatening” conditions submitted to the FDA under investigational-new-drug applications (IND).16 A Web-based registry, ClinicalTrials.gov, was established in 2000 by the National Library of Medicine on behalf of the National Institutes of Health as a result of this law.17,18 Although FDAMA 113 mandates the registration of certain data elements, ClinicalTrials.gov also includes a broad set of optional data elements. In addition, ClinicalTrials.gov permits the registration of any clinical trial, regardless of its IND status, the type of intervention (e.g., surgical procedure, device, or drug), the medical condition, or the country of origin. As of late October 2005, the registry contained more than 23,000 trials.

We examined the completeness and utility of the information contained in trial-registration records in ClinicalTrials.gov from May 20 through October 11, 2005. This period includes time both before and after September 13, 2005, the date of implementation of the International Committee of Medical Journal Editors (ICMJE) policy requiring the registration of clinical trials as a prerequisite for consideration for publication.7,8

Methods

The Registry

Sponsors, principal investigators, or other persons or organizations with primary responsibility for a given clinical trial (called “data providers”) can register with ClinicalTrials.gov through a Web-based system (http://prsinfo.ClinicalTrials.gov). In some instances, “intermediary trial registries,” such as that of the National Cancer Institute (www.cancer.gov), provide trial data. The database uses both open-ended responses and menu-based options, and terms from the National Library of Medicine Unified Medical Language System19,20 are used to facilitate subsequent information retrieval. Trials with the same protocol that are conducted at multiple sites are considered one trial in the registry. The complete entry in the registry for a given trial is referred to as a record in the database.

ClinicalTrials.gov includes both mandatory and optional data elements. Trials cannot be registered without the completion of all mandatory data elements, which include both FDAMA 113 and registry-imposed requirements. In addition, the ICMJE requires completion of some of the optional data elements. Members of the National Library of Medicine staff manage the quality of information in the registry by rejecting records that do not have all required fields completed, reviewing entries for appropriate content and internal consistency, ensuring that links are active and relevant, checking contact information for recruiting studies, and confirming that approval from an institutional review board has been obtained. In addition, sponsoring organizations must elec-
May 20, 2005

**A**

**Observational Trials**

May 20, 2005

2128 Trials

**Interventional Trials**

May 20, 2005

11,025 Trials

Total

May 20, 2005

13,153 Trials

Interval registration

1231 Trials

Interval registration

8330 Trials

Federal
8688 Trials

Industry
2064 Trials

University
273 Trials

Federal
1108 Trials

Industry
2670 Trials

University
4552 Trials

**Interval registration**

October 11, 2005

3359 Trials

October 11, 2005

19,355 Trials

Total

October 11, 2005

22,714 Trials

**B**

**Interventional Non-drug Trials**

May 20, 2005

1533 Trials

**Interventional Drug Trials**

May 20, 2005

9492 Trials

Total

May 20, 2005

11,025 Interventional trials

Interval registration

2324 Trials

Interval registration

6006 Trials

Federal
9796 Trials

Industry
4734 Trials

University
4825 Trials

Interval registration

6006 Trials

Interval registration

2670 Trials

Federal
14,621 Trials

Industry
2064 Trials

University
4825 Trials

Total

October 11, 2005

19,355 Interventional trials

**C**

**Interventional Trials from Nonindustry Providers**

May 20, 2005

2064 Trials

May 20, 2005

14,621 Trials

Total

May 20, 2005

11,025 Interventional trials

Interval registration

5660 Trials

Interval registration

2670 Trials

Federal
9796 Trials

Industry
4734 Trials

University
4825 Trials

Total

October 11, 2005

19,355 Interventional trials
tronically sign off on all entries (and subsequent revisions) before they are made available on the Web site.

**STUDY 1: ALL INTERVENTIONAL TRIALS**

We described the numbers and types of trials registered in ClinicalTrials.gov. Because records in ClinicalTrials.gov can be modified at any time by data providers to keep the information current, this study was conducted with data that were available to the public on May 20, 2005 (before the September 13, 2005, implementation of the ICMJE policy on trial registration) and on October 11, 2005 (four weeks after implementation of the policy). We also reviewed data from trials registered between these two dates, inclusively, which we refer to as the interval sample (Fig. 1A).

Searches of ClinicalTrials.gov were accomplished with the use of a National Library of Medicine reporting tool, although they could be replicated with the use of the public search function in combination with individual inspection of those data.

**STUDY 2: “INTERVENTION NAME” FIELD**

We reviewed ClinicalTrials.gov records to determine patterns of completion for the ICMJE-required data element termed “Intervention Name.” FDAMA 113 mandates completion of this field, although it does not specify how informative the entry must be, thereby limiting our ability to enforce the use of specific drug names.

We reviewed Intervention Name fields to see whether the information provided gave clinically meaningful insight into the specific treatment that was being tested. For example, a preliminary review of records showed that nonspecific terms such as “investigational drug,” rather than the name of the drug under study, were occasionally used. We limited our review of this field to interventional trials of drugs or vaccines (Fig. 1B). Records were considered acceptable if they specified at least one drug name or unique company identifying serial number. We did not evaluate the completeness of information provided about comparison interventions in a study. For example, a record that lists in the Intervention Name field “acetylsalicylic acid compared with active comparator” would have been considered acceptable for the purpose of this study, even though the information contained was not as clinically meaningful as it would have been if specific names for both drugs had been given.

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We first tabulated the number of trials with and without any entry in the Primary Outcome Measure field. We stratified data for the top 20 pharmaceutical companies, ranked according to volume of U.S. drug sales. We examined the relationship between completion of this field and the phase of the study. We also assessed the quality of the entries in this field by noting whether or not they specified a measure and a time point. This subjective assessment was made (by one of us) on a sample of the records for phase 2, 3, and 4 drug studies registered by the top 10 drug companies during the interval between May 20 and October 11.

**STATISTICAL ANALYSIS**

We report primarily descriptive statistics. We used a chi-square test to examine the relationship between completion of the Primary Outcome Measure field and phase of study.

**RESULTS**

**STUDY 1: ALL INTERVENTIONAL TRIALS**

On May 20, 2005, there were 13,153 records in ClinicalTrials.gov; the number had increased to
22,714 as of October 11, 2005. This increase was largely attributable to a spike in registrations during the period immediately before and after September 13, 2005 (Fig. 2). Table 1 contains data on the number of trials registered according to key trial characteristics. There were increases in registered trials from all categories of data providers. The sharpest rise was in the category comprising universities, foundations, and other nongovernmental, nonindustry providers. The number of trials registered by commercial sponsors more than doubled, including an increase in the number of IND studies, from 2010 to 3516, and an increase in the number of non-IND studies, from 77 to 1348. Overall, the number of data providers increased from 667 to 1969 during this time. Among commercial sponsors, the number of companies registering trials rose from 328 to 575; among the latter were all of the top 20 pharmaceutical companies (according to volume of sales in the United States in 2005) and 14 of the top 20 medical-device companies (according to estimated volume of global sales in 2004).

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**STUDY 2: INTERVENTION NAME FIELD**

The Intervention Name field was completed with a specific entry in 100 percent of the nonindustry records at both time points. The percentage of industry records with a nonspecific entry dropped from 10 percent to 2 percent during the study period (Table 2). All the nonspecific entries at both...
time points were attributable to four drug companies: Merck, GlaxoSmithKline, Pfizer, and Lilly. On May 20, 2005, the percentage of trials with nonspecific entries in this field varied from 91 percent (Merck) to 3 percent (Lilly). Between May 20 and October 11, 2005, only two companies, GlaxoSmithKline and Pfizer, created new records with nonspecific intervention names, in 1 percent and 6 percent of their entries, respectively. Merck, GlaxoSmithKline, and Pfizer also added specific information to previously vague entries during the study period; Merck made the most dramatic changes, by reducing their number of nonspecific entries from 91 percent on May 20 to less than 1 percent on October 11 (Table 2). However, on October 11, there were noninformative entries in 21 percent of GlaxoSmithKline records and 11 percent of Pfizer records.

**STUDY 3: PRIMARY OUTCOME MEASURE FIELD**

Use of the Primary Outcome Measure field was assessed in the interval sample only. Information had been entered in this field in 2033 of 2670 records registered by industry (76 percent) during the study interval. Seventy percent of the records (range, 0 percent to 100 percent) from the top 20 drug companies included information in this field (Table 3). The rates of completion of this field were 77 percent for phase 1 studies, 79 percent for phase 2 studies, 76 percent for phase 3 studies, and 65 percent for phase 4 studies ($\chi^2=26.21$, with 3 df; $P<0.001$).

The clinical value of the information provided in the Primary Outcome Measure field varied. Table 4 shows five categories of quality based on the specificity of the information about the primary outcome measure and the inclusion of information about the time it was measured. The 657 phase 2, 3, or 4 records from the top 10 drug companies that had entries in this field were reviewed and assigned to one of these categories. Table 4 shows that 17 percent of the entries were vague, whereas the others had varying degrees of useful information.

**DISCUSSION**

Our findings support the conclusion that ICMJE policy has had an effect on trial-registration practices. Among commercial sponsors, there was an increase in the registration of both IND and non-IND studies. Nonindustry data providers also dramatically changed their registration behavior around the time of the ICMJE deadline. The 73 percent increase in trials registered during this time was associated with a 195 percent increase in the number of data providers from around the world. Since these new providers seem to have registered in order to comply with ICMJE policy, it is likely that they will continue to register trials.

Examination of data-element usage in ClinicalTrials.gov suggests that the act of registration alone is not a good indicator of adherence to registration policies. When trial sponsors have the option of providing information of marginal clinical value in a particular data field, our findings show that some companies provide useful information and others do not. This heterogeneous behavior may indicate varying degrees of comfort with different levels of disclosure. For example, among data elements not examined in this trial, there has been a learning curve, with some companies being slower than others to provide mandatory items such as the name of the sponsor and the location of the trial.\textsuperscript{25}

Completion of the Intervention Name field is mandatory for all trials in ClinicalTrials.gov, but the use of specific terms has not been enforced. We determined that three industry data provid-
### Table 2. Number and Disposition of Records from Industry Providers for Interventional Trials with Nonspecific Entries in the “Intervention Name” Field.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. of trials</td>
<td>Records Corrected with Addition of Company Serial Number</td>
<td>Records Corrected with Addition of Drug Name no.</td>
</tr>
<tr>
<td>Merck</td>
<td>120/132</td>
<td>25</td>
<td>94</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>53/104</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pfizer</td>
<td>22/75</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lilly</td>
<td>3/96</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other industry</td>
<td>0/1619</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>198/2026</td>
<td>29</td>
<td>100</td>
</tr>
</tbody>
</table>

* Specific providers are listed in descending order of the number of nonspecific records as of May 20, 2005.

### Table 3. Use of the “Primary Outcome Measure” Field by 20 Drug Companies from May 20 through October 11, 2005.

<table>
<thead>
<tr>
<th>Rank According to U.S. Drug Sales*</th>
<th>Company</th>
<th>No. of Records with Primary Outcome Measure</th>
<th>Total No. of Records</th>
<th>Percentage of Records with Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pfizer</td>
<td>221</td>
<td>224</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>GlaxoSmithKline</td>
<td>63</td>
<td>66</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Johnson &amp; Johnson</td>
<td>57</td>
<td>63</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Merck</td>
<td>9</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>AstraZeneca</td>
<td>51</td>
<td>52</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>Novartis</td>
<td>8</td>
<td>239</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Amgen</td>
<td>65</td>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>Sanofi–Aventis</td>
<td>19</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Bristol-Myers Squibb</td>
<td>53</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>Lilly</td>
<td>121</td>
<td>136</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>Wyeth</td>
<td>53</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>Abbott</td>
<td>19</td>
<td>34</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>Hoffmann–La Roche</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>TAP Pharmaceutical</td>
<td>22</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>Boehringer Ingelheim</td>
<td>48</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>16</td>
<td>Teva (Teva Neuroscience)</td>
<td>14</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>17</td>
<td>Schering-Plough</td>
<td>1</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>Forest Laboratories</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>19</td>
<td>Eisai</td>
<td>31</td>
<td>35</td>
<td>89</td>
</tr>
<tr>
<td>20</td>
<td>Watson</td>
<td>15</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>Total for the 20 companies</td>
<td>871</td>
<td>1247</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

* Data on rank according to volume of U.S. sales are from IMS Health.²³
The new england journal of medicine

n engl j med 353;26 www.nejm.org december 29, 2005

ers — Merck, GlaxoSmithKline, and Pfizer — used a nonspecific term, such as “investigational drug,” between 29 percent and 91 percent of the time in trials registered as of May 20, 2005. These three companies are ranked in the top five according to volume of U.S. drug sales. Lilly used nonspecific intervention names in 3 of its 96 entries (3 percent). In contrast, other data providers, including 571 other industry providers, entered specific information (either a name or a serial number) in this field in all their records. Between May 20 and October 11, only two drug companies, GlaxoSmithKline and Pfizer, used a nonspecific term in this field, and then only rarely. In addition, many of the previously identified nonspecific records were corrected with the addition of drug names or serial numbers.

Our assessment of the quality of information in the Intervention Name field is limited by our methods. Our search revealed only records that had an easily identified term, such as “investigational drug,” in lieu of a drug name. As a result, entries such as “tyrosine kinase inhibitor” or “antibiotic” were not captured in our search for nonspecific terms. In addition, we were not able to evaluate the degree to which interventions in all groups in a study were delineated. Such information is critical to the full description of a clinical trial. Structures for collecting and monitoring the quality of this information need to be developed.

The Primary Outcome Measure field has been available since October 1, 2004. Before May 20, 2005, this field was commonly left blank by industry and other data providers. Since then, 76 percent of industry records have included an entry in this field, although the percentages vary widely according to company (Table 3). In general, information in this field is more likely to be omitted for phase 4 trials. In addition, the quality and completeness of the entries vary with respect to standard attributes of outcome measures. The attributes presented in Table 4 are consistent with those identified in global standards, such as the Tripartite Harmonised ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline E326 and the ICMJE statement.8 Although we examined only industry records, the use of this field by all data providers will need to be monitored and discussed. It is not clear how ClinicalTrials.gov can best provide information about outcome measures to the full range of interested parties, including patients, clinicians, researchers, and policymakers. In the meantime, more structured guidelines for listing outcome measures might enhance the utility of data in ClinicalTrials.gov and other registries.

Evaluation of compliance with the legal mandate for trial registration, FDAMA 113, shows improving but imperfect compliance on the part of industry.25 Although we cannot judge the degree of compliance with ICMJE policy, which is not

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**Table 4. Attributes of Entries in “Primary Outcome Measure” Field.**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Frequency (N = 657)*</th>
<th>Examples from ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vague</td>
<td>17%</td>
<td>Clinical response Tolerability</td>
</tr>
<tr>
<td>Domain without specific measure</td>
<td>19%</td>
<td>Glucose regulation Severity of symptoms of schizophrenia</td>
</tr>
<tr>
<td>Specific measure without time frame</td>
<td>23%</td>
<td>Intravenous glucose-tolerance test Structured clinical interview — positive and negative syndrome scale No. of hospitalizations</td>
</tr>
<tr>
<td>Time frame without specific measure</td>
<td>10%</td>
<td>Tumor response at 3 mo Freedom from progression at 2 yr Improvement in glucose control over 16-wk period</td>
</tr>
<tr>
<td>Specific measure and time frame</td>
<td>31%</td>
<td>Change in glycosylated hemoglobin from baseline to 6 mo Mortality from any cause at 30 days</td>
</tr>
</tbody>
</table>

* Frequencies are based on a review of 657 records from the top 10 drug companies, ranked according to data from IMS Health on the volume of U.S. sales.23 Phase 2, 3, and 4 trials were included.
legally binding, without knowing the number of clinical trials overall, our data indicate large increases in trial registration from all sectors. Some commercial organizations and other stakeholders note that the mandatory registration of exploratory trials (roughly, phase 1 and 2 trials) and the prospective disclosure of certain data elements, including intervention name and primary outcome measure, raise critical proprietary issues. These concerns may explain some of the variations in registration practices that are evident in our data.

Supported by the Intramural Research Program of the National Library of Medicine, National Institutes of Health.

We are indebted to Anne M. Bergeris for assistance with sample selection, data analysis, and comments on drafts of the manuscript; to In Hye Cho for assistance with data analysis; and to Drs. Donald A.B. Lindberg and Stephen G. Pauker for review of drafts of the manuscript.

REFERENCES


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A 37-year-old man was evaluated because of a two-year history of asymptomatic thickening and darkening of the skin on his axillae (Panel A), neck, face, and arms. The patient had no history of diabetes mellitus or other endocrine disorders, alcohol abuse, or chronic hepatitis. On examination of the skin, brown patches and plaques with elevated ridges and a velvety feel were observed on the axillary regions, the neck, the antecubital fossae, the dorsal aspect of the hands, and the malar and periorbital regions. Cutaneous findings were consistent with the diagnosis of acanthosis nigricans. An evaluation for cancer revealed a hepatic mass, 20 by 17 cm. The patient underwent right hepatic lobar resection. Histopathological examination of the resected tissue showed a moderately differentiated hepatocellular carcinoma with extensive hemorrhagic, necrotic, and sclerotic areas (T2N0M0). Three months after surgery, a spontaneous complete regression of cutaneous lesions occurred (Panel B). Malignant acanthosis nigricans is a rare form of acanthosis nigricans that precedes or occurs in association with often aggressive internal cancers and usually correlates with the evolution of the underlying neoplasm.

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WEB-ONLY IMAGES IN CLINICAL MEDICINE
Click on “Recent Featured Images” at www.nejm.org to see the Journal’s Web-only Images in Clinical Medicine. The Images are listed (with page numbers) in the table of contents of the printed Journal the week they are published and are compiled on the Journal’s Web site.
An 18-year-old man was referred by his dentist to the oral and maxillofacial surgery clinic of this hospital because of left mandibular swelling.

One month earlier, the patient first noticed gradual left mandibular enlargement without pain, fever, malocclusion, sensory changes, or trismus. There was no history of trauma or recent dental work. He had no illnesses or allergies, took no medications, did not use tobacco or alcohol, and reported no first-degree relatives with cancer.

On physical examination, there was obvious facial asymmetry, with the left side of the jaw larger than the right (Fig. 1A). A firm, nontender swelling was palpable along the ramus and posterior body of the left mandible. Neurologic examination revealed normal function of cranial nerves V and VII. He had generalized, mild-to-moderate gingivitis on intraoral examination; the mucosae and soft tissues were otherwise normal. The dentition was intact and in good repair, and there was no malocclusion. There was expansion of the bone along the left lateral alveolar ridge of the mandible, which obliterated the buccal vestibule (Fig. 1C).

A panoramic radiograph of the jaws revealed a septated radiolucent lesion in the left mandible. Four days later, a maxillofacial computed tomographic (CT) scan obtained without intravenously administered contrast material showed a unilocular, expansile, lytic lesion, 5.1 cm (superoinferior) by 2.6 cm (buccolingual) by 8 cm (mesiodistal), in the left mandible.

A diagnostic procedure was performed.

**DIFFERENTIAL DIAGNOSIS**

*Dr. Meredith August:* I was involved in the care of this patient and am aware of the diagnosis. This case presents an opportunity to review the differential diagnosis and management of cystic lesions of the jaw. May we review the imaging studies?

*Dr. Paul A. Caruso:* A panoramic radiograph of the jaws obtained at the time of the patient's presentation (Fig. 2A) revealed a large, expansile, partially septated, radiolucent lesion of the left mandible that extended from the midbody mesially to
the ramus distally, involved the sigmoid notch and the base of the coronoid process, and spared the condyle. The lesion displaced the impacted left mandibular third molar mesially, inferiorly, and buccally; involved both the crown and the roots; and clearly involved the tooth beyond the cemento-enamel junction. The lesion resorbed the distal roots of the left mandibular first molar.

A non-contrast-enhanced, maxillofacial CT with three-dimensional reconstructions (Fig. 1A, 1B, and 1C of the Supplementary Appendix, available with the full text of this article at www.nejm.org) showed a partially septated, otherwise homogeneous-appearing, radiolucent lesion in the left mandible that thinned and expanded but did not breach the lingual and buccal cortices, and showed no extraosseous component.

Dr. August: This 18-year-old, otherwise healthy man presented with a one-month history of swelling in the left jaw that was not associated with pain, fever, trismus, malocclusion, antecedent trauma, or neurosensory change. A physical examination ruled out an odontogenic source of infection; his teeth were in good repair. The panoramic radiograph revealed a large and localized radiolucency of the left mandible with inferior displacement of the left mandibular third molar and evidence of root resorption of the left mandibular second molar. CT scanning showed that the buccal and lingual cortices were expanded but intact. Both odontogenic and nonodontogenic processes are included in this differential diagnosis (Table 1).

**Figure 1. Clinical Images of the Patient.**

Images of the face when the patient presented (Panel A) and 21 months after the first procedure (Panel B), showing swelling of the left mandible (Panel A, arrow), which is greatly diminished in Panel B. An intraoral photograph, also obtained at the time of presentation (Panel C), shows smooth thickening of the posterior body and ramus of the left mandible (arrows) that obliterate the buccal vestibule. Another intraoral image obtained 21 months after the first procedure (Panel D) shows substantial reduction in swelling.

**ODONTOGENIC CYSTS AND NEOPLASMS**

Because of the regular bony contours of the radiolucency on imaging studies and the associated impacted tooth, an odontogenic cyst is the most likely problem. Dentigerous cysts are the most common odontogenic cysts in this location; they are associated with the displacement of impacted teeth and cortical expansion. The odontogenic keratocyst represents 10 percent of all cystic jaw lesions; the posterior mandibular location, seen in this case, is most common, and 50 percent of these cysts are associated with impacted teeth. Pain and paresthesias are uncommon for both dentigerous cysts and odontogenic keratocysts. Root resorption is more commonly reported with dentigerous cysts. The calcifying odontogenic cyst usually has...
variable amounts of radiopaque material within it but in early phases may present as a primarily lucent lesion. Less common odontogenic cysts, such as the glandular odontogenic cyst, should also be considered in the differential diagnosis.

Benign odontogenic tumors can also present as multiloculated radiolucent lesions. Both ameloblastomas and ameloblastic fibromas are commonly found in this location. The average age of a patient at diagnosis for ameloblastoma is in the third decade and somewhat younger for ameloblastic fibroma. Both tumors tend to expand rather than perforate bone, as does this lesion. They are seldom painful and are commonly multilocular on radiographs. Unicystic ameloblastoma accounts for about 10 percent of intraosseous ameloblastomas. Most are found in the mandible and have features that are radiographically identical to those in this case. Another possibility, the calcifying epithelial odontogenic tumor, is more common in middle-aged patients and often is first noticed as a painless swelling of the mandible. Its radiographic pattern is variable (often containing calcifications), but a loculated radiolucency with an associated impaction has been described. The odontogenic myxoma is most common in patients who are in their teens and 20s and has a slight predilection for the mandible. Swelling without pain or tooth displacement is common. Bony perforation is rare. In early stages, a myxoma as visualized by radiography can show a well-circumscribed radiolucency. The squamous odontogenic tumor may be found in patients of widely varying ages. The bicuspid and molar regions are the most common locations for this type of tumor, which is generally painless and radiographically associated with the junction of the crown and the root of an impacted tooth.

### Table 1. Cystic Lesions of the Mandible.

<table>
<thead>
<tr>
<th>Odontogenic lesions</th>
<th>Cystic Lesions of the Mandible.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentigerous cyst</td>
<td>Cysts</td>
</tr>
<tr>
<td>Odontogenic keratocyst (now considered to be a neoplasm)</td>
<td>Odontogenic keratocyst (now considered to be a neoplasm)</td>
</tr>
<tr>
<td>Calcifying odontogenic cyst</td>
<td>Calcifying odontogenic cyst</td>
</tr>
<tr>
<td>Glandular odontogenic cyst</td>
<td>Glandular odontogenic cyst</td>
</tr>
<tr>
<td>Ameloblastoma</td>
<td>Tumors</td>
</tr>
<tr>
<td>Ameloblastic fibroma</td>
<td>Calcifying epithelial odontogenic tumor</td>
</tr>
<tr>
<td>Calcifying epithelial odontogenic tumor</td>
<td>Squamous odontogenic tumor</td>
</tr>
<tr>
<td>Squamous odontogenic tumor</td>
<td>Nonodontogenic benign tumors</td>
</tr>
<tr>
<td>Aggressive giant-cell tumor</td>
<td>Nonodontogenic benign tumors</td>
</tr>
<tr>
<td>Ossifying and cementifying fibromas</td>
<td>Nonodontogenic benign tumors</td>
</tr>
<tr>
<td>Desmoplastic fibroma</td>
<td>Nonodontogenic benign tumors</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>Nonodontogenic benign tumors</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>Nonodontogenic benign tumors</td>
</tr>
</tbody>
</table>

Figure 2. Imaging Studies of the Mandibular Lesion.

A preprocedural panoramic radiograph (Panel A) reveals an expansile, lytic lesion involving the body and ramus of the left mandible that incorporates the unerupted mandibular third molar. A panoramic radiograph obtained 13 months after the biopsy (Panel B) shows two irrigation cannulae, thick marginal sclerosis, and mineralization within the lesion but persistent central radiolucency, most notably within the ramus. A panoramic radiograph obtained three months after the second procedure (Panel C) shows marked progressive sclerosis of the entire lesion.
NONODONTGENIC TUMORS

One type of benign nonodontogenic tumor to be considered in this case is an aggressive giant-cell tumor. A loculated radiolucency on radiography is typical, and cortical thinning and displacement of teeth are common. The patient’s age is consistent with this diagnosis. Ossifying and cementifying fibromas are generally found in slightly older patients. Swelling without pain is common. Bone perforation is rare. On radiographic examination, the lesions are well circumscribed and radiolucent in early stages. Aneurysmal bone cysts could also have these signs and symptoms, although pain is more frequently associated with cases of this type of tumor. Desmoplastic fibroma (an intrabony form of aggressive fibromatosis) is a rare tumor, but the patient’s age and the location of the lesion, as well as the radiographic findings, make it a possibility.

Vascular malformations need to be considered. The absence of any bleeding history, bruit, or thrill and no involvement of the overlying mucosa or skin make these unlikely to be the final diagnosis. Malignant tumors (both primary and metastatic) would be far down on the list of differential diagnoses. The radiographic regularity, along with the lack of neurosensory change or pain, make these tumors unlikely to be the cause of this patient’s symptoms.

The findings in this case of an 18-year-old man with painless left posterior mandibular swelling with radiographic findings of a loculated radiolucency and an associated impacted tooth favor the diagnosis of an odontogenic cyst. The dentigerous cyst is far more common than the odontogenic keratocyst. Both lesions have a predilection for this mandibular location. However, the lack of bone perforation, especially with a lesion this large, as well as the circumferential appearance of the radiolucency surrounding the impacted tooth rather than emanating from the junction of the crown and the root, slightly favor the diagnosis of odontogenic keratocyst. Nonetheless, a dentigerous cyst and some of the less common odontogenic and nonodontogenic tumors cannot be ruled out. A biopsy of the lesion is necessary to establish the diagnosis.

Standard biopsy techniques require opening the cyst cavity and removing a portion of the lining for evaluation. This procedure often converts a closed cavity into an infected and open lesion with communication to the oral cavity. It may make eventual removal of the lesion more difficult and affect the accuracy of the diagnosis on the final specimen. Fine-needle aspiration biopsy in conjunction with immunocytochemical staining for low-molecular-weight cytokeratin has proved useful in sampling cells that line the cyst and in helping to establish a preoperative diagnosis, specifically, by differentiating dentigerous from odontogenic keratocysts. In this patient, fine-needle aspiration with cytokeratin staining would be appropriate. Because of the high clinical likelihood that this is an odontogenic keratocyst, open biopsy with frozen-section diagnosis, followed by preparation for subsequent definitive therapy, could also be considered.

DR. MEREDITH AUGUST’S DIAGNOSIS

Odontogenic keratocyst.

PATHOLOGICAL DISCUSSION

Dr. Edward T. Lahey (Department of Oral and Maxillofacial Surgery): The diagnostic procedure was an incisional biopsy of the lesion. The lesion was aspirated first, yielding a cloudy yellow fluid that was not bloody; ruling out a vascular malformation is imperative before opening into a bony cavity. Electrocautery was used to incise the mucosa from the left external oblique ridge, anterior to the first molar. A full-thickness mucoperiosteal flap was then elevated to reveal perforation of the lesion through the left lateral mandibular cortex, posterior to the second molar. Bone was removed in this region, exposing a lined cavity. A portion of the lining was removed for intraoperative frozen-section evaluation.

Dr. William C. Faquin: The biopsy specimen of the left mandible was sent for intraoperative frozen-section examination. The diagnostic information obtained by frozen section would be used to guide the surgical management. Microscopical examination revealed a fragmented cystic lesion with a dense fibrous wall, lined by a stratified squamous epithelium that was approximately six to seven cells thick (Fig. 3A). Occasional smaller (daughter) cysts were present within the fibrous wall (Fig. 3B). The interface between the epithelium and stroma was smooth, lacking the rete pegs that characterize normal squamous mucosa. The basal layer of the epithelium consisted of a palisaded arrange-
ment of cuboidal cells with dark nuclei, and the epithelial surface showed a wavy layer of keratinized cells with retained nuclei, known as a corrugated parakeratinized layer (Fig. 3C). The cyst lumen contained sloughed parakeratotic cells and anucleated squamous cells. A diagnosis of an odontogenic keratocyst was made.

On permanent, paraffin-embedded sections, an immunohistochemical stain for keratin 10 showed positive reactivity of the surface parakeratinized layer as well as of the cyst contents (Fig. 3D). On the basis of these microscopical findings, the frozen-section diagnosis of an odontogenic keratocyst was confirmed.

The odontogenic keratocyst is a squamous-epithelium-lined cystic neoplasm thought to be from the dental lamina or the primordial odontogenic epithelium. Odontogenic keratocysts are locally destructive lesions that frequently recur and that rarely can be associated with epithelial dysplasia or even squamous-cell carcinoma. Evidence that the tumor-suppressor gene, PATCHED, is mutated in both inherited and sporadic forms of the parakeratinized type of odontogenic keratocyst supports the view that unlike other odontogenic cysts, odontogenic keratocysts are neoplasms.

The histologic diagnosis of an odontogenic keratocyst is based primarily on the presence of specific microscopic features: a thin, stratified squamous epithelium with a prominent palisaded basal layer; a smooth interface with the stroma, lacking rete pegs; and a wavy or corrugated parakeratinized surface layer. Immunohistochemical staining for keratin 10, a low-molecular-weight cytokeratin that is expressed in a subset of kera-
tinocytes within normal gingival mucosa, shows a characteristic strong staining of the superficial parakeratinized cells of odontogenic keratocysts and can be applied to both histologic and cytologic samples as an ancillary marker to support the diagnosis of an odontogenic keratocyst (Fig. 3D).

The entity most commonly confused clinically and microscopically with an odontogenic keratocyst is the dentigerous cyst, which is characterized by a squamous lining of variable thickness, sometimes with rete pegs; scattered mucin-containing cells; and occasionally ciliated cells — features not seen in odontogenic keratocysts. However, when an odontogenic keratocyst becomes inflamed, its epithelium may become indistinguishable from that of a dentigerous cyst. In any odontogenic cyst, thorough sampling by the surgeon and adequate sectioning of the biopsy specimen by the pathologist are essential. Apparently, dentigerous cysts that recur are typically found to have been odontogenic keratocysts whose diagnostic features have been obscured by inflammation or inadequate sampling.

Approximately 5 percent of odontogenic kerato- cysts are associated with the autosomal dominant basal cell nevus syndrome (Gorlin’s syndrome), associated with germ-line mutations in PATCHED and characterized by multiple basal-cell carcinomas of the skin, multiple odontogenic keratocysts of the jaw, skeletal abnormalities such as bifid ribs, and occasionally by other tumors, such as medulloblastomas and ovarian fibromas.

**DISCUSSION OF MANAGEMENT**

*Dr. August:* Management of an odontogenic keratocyst is a focus of investigation, because of the high recurrence rate (overall, about 30 percent). En bloc resection will prevent recurrences but results in clinical deformity and the necessity for bone-graft reconstruction.

Enucleation — removal of the cyst lining — is the most common method of treatment, but because the lining is typically thin and friable, it often fragments during the removal process. Incomplete removal of the cyst lining and associated connective tissue with microcysts is thought to predispose the patient to recurrence or persistence of the tumor. Curettage, cryotherapy, peripheral ostectomy, and application of chemical fixatives to the underlying bone all lower recurrence rates but result in increased morbidity.

A protocol of surgical decompression of the cyst, followed by 12 months of twice-daily irrigation with hexachlorophene and, later, cystectomy, has proved to be a promising approach for large odontogenic keratocysts. The decompression prevents further expansion, while the irrigant causes the neoplastic epithelium to undergo squamous metaplasia and the cyst wall to become fibrotic, thus minimizing the likelihood of recurrence and facilitating subsequent removal of any residual lesion. In patients who undergo this treatment, there is often a change in the character of the cyst lining seen at eventual cystectomy; it may have become thickened and less adherent to the underlying bone, and in about 60 percent of cases, the epithelium no longer showed the features of odonotogenic keratocyst and was cytokeratin-10 negative. The reported recurrence rate with this treatment has been less than 10 percent.

*Dr. Lahey:* After the intraoperative diagnosis of an odontogenic keratocyst was made, the cyst was explored along its entire extent to ensure that no septa remained intact. Two decompression stents were inserted into the cystic cavity and securely fastened to the reapproximated mucosal wound edges (Fig. 2 of the Supplementary Appendix). The patient was discharged to his home later the same day with instructions to irrigate the cyst twice daily through the irrigation tubes using 10 ml of 0.12 percent chlorhexidine.

The patient was initially seen in the clinic weekly for a physical examination and to obtain panoramic radiographs. Three weeks after he went home, there was a purulent discharge from the posterior stent. The patient admitted that he had not adhered to the prescribed irrigation regimen. Penicillin was prescribed for one week, and he was counseled regarding the irrigation protocol. After the first four weeks, the patient was followed monthly.

After 21 months, a physical examination showed vastly reduced facial asymmetry, with only a slight fullness on the left (Fig. 1B). Intraoral examination showed the resolution of the left mandibular vestibular swelling (Fig. 1D). Reexploration and enucleation of the residual lesion was performed according to the protocol. The patient was discharged to his home on the day of the cystectomy. At three-month and six-month follow-ups, he had only mild, residual facial swelling on the lower left side.
Dr. Faquin: Microscopic examination of the resection specimen revealed inflamed, dense fibrotic stroma and a small, 1.0-cm squamous-epithelium-lined cyst (Fig. 3 of the Supplementary Appendix). Focal areas of the cyst lining revealed classic features of an odontogenic keratocyst, whereas other areas of the epithelial lining were thicker, without a distinct basal layer or parakeratotic surface.

Dr. Caruso: A panoramic radiograph obtained 13 months after the first procedure (Fig. 2B) showed progressive sclerosis of the lesion, most notably along the margins of the mesial component of the lesion nearest the irrigation cannulae; there was a persistent radiolucency in the center, most conspicuous within the distal components of the lesion. A panoramic radiograph obtained three months after the second procedure (Fig. 2C) showed marked sclerosis and new bone formation within the mesial and distal components of the lesion, indicating essentially complete resolution of the lesion.

A Physician: Is it possible to use keratin 10 to distinguish between a dentigerous cyst and an inflamed odontogenic keratocyst?

Dr. Faquin: Immunohistochemical staining of odontogenic keratocysts using keratin 10 works best when you have well-defined histologic features of an odontogenic keratocyst, so that in an inflamed lesion, the keratin-10 staining is less likely to give a definitive result. I think that the best application for keratin 10 is in a fine-needle aspiration in which there are only squamous cells, which could be either from a dentigerous cyst or from an odontogenic keratocyst. If the cells are keratin-10–positive, that would support the diagnosis of an odontogenic keratocyst.

Dr. August: Case selection is important, and the radiographic features help in planning. If there are a lot of loculations, we try to identify them and break them up if possible or, as in this patient, place two stents in a very large lesion. It is important to make sure that the whole cyst receives the effect of treatment, so loculations within the cavity must be recognized and removed, if possible. Finally, the patient must be able to understand the irrigation instructions and be willing to comply with the procedure.

A N AT O M I C A L D I A G N O S I S

Odontogenic keratocyst.

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

REFERENCES


SLIDE SETS FOR THE CASE RECORDS AVAILABLE IN DIGITAL FORMAT

Any reader of the Journal who uses the Case Records of the Massachusetts General Hospital as a teaching exercise or reference material is eligible to receive digital images, with identifying legends, of pertinent radiographic, neurologic, and cardiac studies, gross specimens, and photomicrographs. The images on the CD for each case are in both PowerPoint and 300 dpi jpg format. For some cases, additional images that have not been selected for publication will be included on the CD. These images, which illustrate the current cases in the Journal, are mailed from the Department of Pathology to correspond to the week of publication and may be retained by the subscriber. Each year approximately 250 images from 40 cases are sent to each subscriber. The cost of the subscription is $450 per year. Application forms for the current subscription year, which began in January, may be obtained from the Lantern Slides Service, Department of Pathology, Massachusetts General Hospital, Boston, MA 02114 (telephone 617-726-2974) or Pathphotoslides@partners.org.

Images from individual cases may be obtained at a cost of $35 per case.
Aromatase Inhibitors — A Triumph of Translational Oncology

Sandra M. Swain, M.D.

Great strides have been made in the diagnosis and treatment of early-stage breast cancer, thanks to advances in molecular medicine, interdisciplinary treatment, and rapid electronic communication. Hormonal therapy, the first and most successful targeted therapy for breast cancer, has saved many thousands of lives. Moreover, screening and adjuvant (postoperative) therapy have increased survival among women with breast cancer.\(^1\)\(^2\) The improvement in survival can be attributed to both adjuvant tamoxifen therapy and adjuvant chemotherapy and has been found in all subgroups of patients regardless of the presence or absence of tumor cells in draining lymph nodes, including women who are premenopausal, those who are postmenopausal, those with estrogen-receptor–negative tumors, and those with estrogen-receptor–positive tumors. Experts are now in the process of classifying breast cancer, which actually consists of a heterogeneous group of cancers, into multiple categories. It is essential to define each subgroup precisely and to delineate distinct characteristics and targets that will lead to tailored therapies that are better than the ones we have now.

In this issue of the *Journal*, the Breast International Group (BIG) 1-98 Collaborative Group reports on a randomized comparison of letrozole, an aromatase inhibitor, with tamoxifen as adjuvant therapy for postmenopausal women with early-stage breast cancer. Their findings validate the results of previous studies showing that aromatase inhibitors were more efficacious than tamoxifen in such women.\(^3\) The BIG 1-98 Collaborative Group found a reduction in the incidence of relapse of 3.4 percentage points at five years in the letrozole group, as compared with the tamoxifen group, after a median follow-up of 25.8 months. The incidence of both distant recurrence and contralateral breast cancers was reduced. The benefit was greatest in patients who had also received chemotherapy, who did not receive radiotherapy, and who had positive nodes. Longer follow-up is important to define the benefit of letrozole in patients with node-negative disease. There was no significant difference in survival between the two groups, but at this point, fewer deaths have occurred among women assigned to letrozole.

Five other large trials have also evaluated aromatase inhibitors. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, with a median follow-up of 68 months, found that, as compared with tamoxifen, adjuvant treatment with anastrozole reduced the recurrence rate by 3.7 percentage points in patients with hormone-receptor–positive tumors.\(^4\) The MA.17 trial, in which women first received tamoxifen for five years and then were randomly assigned to receive placebo or letrozole, found that letrozole improved disease-free survival by 4.6 percentage points, after a median follow-up of 30 months, with a survival difference in the node-positive group only.\(^5\) The Intergroup Exemestane Study (IES), with a median follow-up of 30.6 months, compared 2 to 3 years of tamoxifen followed by 2 to 3 years of exemestane with 5 years of tamoxifen therapy and found that the former regimen increased disease-free survival by 4.7 percentage points.\(^6\) The Italian Anastrozole Trial (ITA), with a median follow-up of 36 months, compared 2 to 3 years of tamoxifen followed by 2 to 3 years of anastrozole with 5 years of tamoxifen and found that sequential treatment re-
duced recurrent-free survival by 5.8 percentage points. Finally, a combined analysis of data from two prospective, multicenter, randomized trials (the Austrian Breast and Colorectal Cancer Study Group trial 8 plus the Arimidex–Nolvadex study) compared women who received two years of tamoxifen followed by three years of anastrozole with women who were given tamoxifen for five years. After a median follow-up of 28 months, sequential therapy was associated with an event-free survival rate that was 3.1 percentage points higher than the rate associated with tamoxifen alone. These five studies varied with respect to the number of women with hormone-receptor–positive tumors, node-negative tumors, and node-positive tumors and the definition of outcomes. It is clear, however, that these trials, with close to 30,000 participants, consistently demonstrate that treatment with an aromatase inhibitor alone or after tamoxifen treatment is beneficial. The questions that remain are the optimal duration of treatment with an aromatase inhibitor, whether tamoxifen or an aromatase inhibitor should be given first, whether sequential treatment is optimal, which aromatase inhibitor is best, and whether an aromatase inhibitor is beneficial for premenopausal women after ovarian ablation. The decrease in contralateral cancers among women treated with an aromatase inhibitor has important implications for chemoprevention. Ongoing trials should answer each of these questions.

One of the most exciting aspects of the findings of these evaluations of aromatase inhibitors is that an animal model predicted the results. In tumor cells and peripheral tissues in postmenopausal women, estrogen is synthesized by aromatase from androstenedione and testosterone. A mouse model was developed to simulate the hormonal milieu in postmenopausal women and used to investigate the ability of aromatase inhibitors and tamoxifen to hinder the growth of breast-cancer cells. This model predicted a superior clinical outcome with aromatase inhibitors. The same model also predicts that the administration of letrozole alone will be more effective than the sequential administration of tamoxifen and letrozole. Future analyses of the continued follow-up of the BIG 1-98 study, which includes a group randomly assigned to receive letrozole before tamoxifen therapy and a group assigned to receive letrozole after tamoxifen therapy, will answer this important question.

A hypothesis developed from the ATAC study is that estrogen-receptor–positive, progesterone-receptor–negative tumors are more susceptible to anastrozole than tumors that have both types of hormone receptors. Although this hypothesis was not supported by the findings of the BIG 1-98 study, because of the relatively short follow-up and multiple subgroup analyses in the study, the idea also cannot be ruled out. Data that support a differential benefit in patients with progesterone-receptor–negative tumors include the finding that patients with such tumors are likely to have HER-1–positive or HER-2–positive breast cancer, positive nodes, tumors with high rates of proliferation and aneuploidy, and lower median levels of estrogen receptors. All these features are typical of an aggressive tumor. Another area of fertile research is the crosstalk between growth factor signaling pathways and the estrogen receptor. This crosstalk may result in tamoxifen resistance by potentiating agonist properties of tamoxifen.

It is clear that unlike tamoxifen, aromatase inhibitors are not associated with an increased risk of thromboembolism or uterine cancer. The incidence of fractures and arthralgias is, however, increased among women taking these inhibitors. Both complications are the result of estrogen deficiency, and they require a thorough evaluation with the aim of limiting these adverse effects. In the BIG 1-98 study, the incidence of serious cardiac events was significantly higher among women given letrozole than among those given tamoxifen. An increase in cardiovascular events among patients receiving an aromatase inhibitor has also been suggested in the IES and ATAC studies. This finding may be due to a cardioprotective effect of tamoxifen, but whatever the mechanism, the potential for adverse cardiovascular events needs close and careful evaluation.

We have seen a substantial increase in the number of patients with small, node-negative tumors over the past several years. In the future, molecular characterization of individual tumors will assist in determining the metastatic potential of the tumor and its sensitivity to various agents. It is our responsibility as physicians to determine the appropriate adjuvant treatment for patients.
but the choices are increasingly complex. Fortunately, we have the results of large, prospective, well-designed, and well-executed clinical trials, such as BIG 1-98, to facilitate our recommendations. We await longer follow-up from all the studies to enable us to offer patients sound advice regarding the benefits and long-term risks of aromatase inhibitors. Meanwhile, all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease.

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

From the Breast Cancer Section, Center for Cancer Research, National Cancer Institute, Bethesda, Md.


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**Trial Registration Report Card**

Jeffrey M. Drazen, M.D., and Alastair J.J. Wood, M.D.

One measure of medical progress is new treatments. The discovery of a novel therapy takes time and money, but more important, it requires the mutual effort of groups that, while they share the common goal of improved treatment, often have fundamentally competing interests. These interests intersect at the clinical trial. Patients who are looking for more effective and safer treatment agree to take part in a clinical trial in the hope that they will benefit from such treatment or that others with similar conditions will benefit later. The company developing the new therapy shares the hope that the trial will be successful, because it wants to market the tested therapy exclusively and profitably for as long as possible before its competitors can launch a similar therapy into the marketplace. These goals, though overlapping, are inevitably in conflict and will generate tension. Such tension has been thrown into sharp relief over the past 15 months by the push for clinical trial registration.

The academic establishment and patients have argued that when patients, motivated by altruism, participate (or even consider participating) in a clinical trial, they are entitled to understand fully all the options available to them in the various trials that are currently recruiting subjects. In addition, their participation in a clinical trial should result in generalizable knowledge that will be available to future patients and investigators to improve patient care. This can happen only when appropriate details of the clinical trial are made available to the public in a timely fashion. The Internet and public registries have made this possible.

Some in industry have argued that to open
their portfolio of clinical trials to public scrutiny, particularly the scrutiny of other drug companies, would put them at such a competitive disadvantage that they would be unable to bring new products to market. Congress, however, decided to encourage openness by enacting on November 21, 1997, Section 113 of the Food and Drug Administration Modernization Act (FDAMA 113). The Section 113 ultimately created ClinicalTrials.gov as an Internet-based public resource for information on studies of drugs, including biologic drug products, that are conducted under the FDA's investigational-new-drug regulations and involve the treatment of serious or life-threatening diseases and conditions.

In September 2004, the International Committee of Medical Journal Editors (ICMJE) announced that its journals would not publish the results of any ongoing trial that had not been appropriately registered in ClinicalTrials.gov or another qualified public registry by September 13, 2005. In this issue of the Journal, Zarin et al. provide a report card on compliance with these legislative and ICMJE requirements and the quality of the reporting that occurred before and after the ICMJE deadline for clinical trial registration. This report card examines whether the data fields required by FDAMA 113 have been completed in a meaningful fashion, with details about the drug or other intervention being studied and the prespecified measure of the trial's primary outcome. Without such critical data, registration becomes meaningless.

Zarin et al. show that there was a dramatic change in the number of trials registered during the summer of 2005. There can be no doubt that this spike was related to the ICMJE statement and deadline, because the rate of registration fell (though to a rate higher than that before the statement) after the deadline for registration passed. In addition, they show that the Intervention Name field was universally completed in a meaningful fashion when the trials were sponsored by academic institutions or the National Institutes of Health. In contrast, among trials registered by commercial sponsors, compliance with this field was variable. Here the message is more nuanced.

The vast majority of commercial entities provided meaningful data in most of their entries before the ICMJE statement and continued to do so during the summer of 2005. However, in the spring, some companies, such as Merck, GlaxoSmithKline, and Pfizer, provided meaningful entries in the Intervention Name field in an astonishingly low number of registrations. During the summer, Merck amended most of its meaningless entries to include clinically useful information in this field; by October they were in compliance in more than 99 percent of their registrations. GlaxoSmithKline and Pfizer are still using meaningless entries in the Intervention Name field in 21 percent and 11 percent of entries, respectively. This is puzzling, since most other companies are able to comply fully with the requirements of FDAMA 113.

The second critical measure examined by Zarin et al. was the number of records with the Primary Outcome field completed. Here the data are less reassuring, and the performance of some companies remains abysmal. Note, by October 2005, Novartis had completed this field only 3 percent of the time, and Merck only 20 percent of the time. Again, many of their competitors were in virtually full compliance, undercutting any argument that this failure reflects a commercial imperative.

The ICMJE requirement that clinical trials be registered if they are to be considered for publication has been a resounding success. But the report cards for some companies would read “improved but could do better.” We demand complete compliance, because trial registration makes moral sense. When patients put themselves at risk to participate in clinical trials, they do so with the tacit understanding that their risk is part of the public record, not merely the secret record of the sponsor.

In our opinion, it is unacceptable for a trial sponsor not to register its trial in a complete, meaningful, and timely fashion. We call for all clinical investigators and patients to participate only in fully registered trials. This call has recently been echoed by the major organization representing academic medical centers in the United States — the Association of American Medical Colleges. If a company continues to register trials using meaningless data, with no respect for the registration process and the patients who participate in those trials, investigators and patients should refuse to participate. If a company realizes that secrecy and failure to
Registries and Registration of Clinical Trials
Charlotte Haug, M.D., Peter C. Gøtzsche, M.D., and Torben V. Schroeder, M.D.

The arguments in favor of the registration of clinical trials are now familiar.\textsuperscript{1-4} Chief among these addresses the practice of selective reporting, whereby negative or detrimental studies are not brought into the public domain, which experts on the subject of clinical trials consider an important form of scientific misconduct.\textsuperscript{5} This practice, as illustrated in a number of high-profile examples, has increased the demand for the mandatory public registration of clinical trials. Registration of trials should improve the completeness, reliability, and quality of the interpretation of clinical research.

This need for registration prompts the question of where trials should be registered. It seems obvious that, to avoid conflicts of interest and to increase the public trust, the entities that establish and manage registries should meet certain requirements. One set of such requirements, as established by the International Committee of Medical Journal Editors (ICMJE),\textsuperscript{6} requires that registries be owned and operated by not-for-profit entities, that they contain a minimal, clinically directive data set,\textsuperscript{7} and that they be electronically searchable, without charge, by any interested party. Originally, only ClinicalTrials.gov, a public registry that was set up to fulfill the legislative requirement mandating the registration of U.S. clinical trials involving patients with serious and life-threatening diseases, met these requirements. At first, this database was limited to clinical trials sanctioned by a U.S. entity, but as of the fall of 2004, it began including clinical trials from anywhere in the world. Even so, many European researchers were reluctant to use ClinicalTrials.gov as a locus for trial registration; an article by Zarin et al. in this issue of the \textit{Journal}\textsuperscript{8} provides a report card on this registry. Many investigators already register their trials in national or European databases, but unfortunately, no pan-European agreement has been struck with regard to how to move forward with public registration of clinical trials.\textsuperscript{9} Through the European Clinical Trials Directive (Directive 2001/20/EC), the European Union introduced legislation requiring the registration of “clinical trials on medicinal products for human use” in a European database. Since May 2004, all clinical trials conducted in member states of the European Union had to be registered in the EudraCT database, supervised by the European Medicines Agency. This registry is confidential and open only to regulatory agencies and organizations that provide funding for research.

A private company, Current Controlled Trials, which is based in the United Kingdom, developed the International Standard Randomised Controlled Trial Number (ISRCTN) scheme. It was launched on a pilot basis in 2000 and formally began operations in May 2003. The goal of this system is to simplify the identification of trials and provide a unique number that can be used to track all publications and reports resulting from each trial. This registry charges a minimal fee to registrants but is free to all who search its contents. This past September, ownership of the database was transferred to a not-for-profit entity, and it now meets all the ICMJE registration requirements.

In addition to EudraCT and ISRCTN, publicly accessible national registries of clinical trials

\textsuperscript{1} Public Health Service Act, 42 U.S.C. § 282(j).
\textsuperscript{2} Investigational New Drug Application, 21 C.F.R. 312.
have been established in several European countries, Japan, and Australia. There has also been a proliferation of registries based on trials involving specific diseases. In addition to public registration, the confidential registration of most clinical trials already exists in France, Italy, Spain, and the Netherlands. If these databases were open to the public, a wealth of information would be unearthed.

Although the desire for regional and specialized registries may be understandable, it is important for all such registries to contain uniform data elements and to be linked electronically — and even better, to share data — so that a search for trials that meet certain criteria would automatically cover all trial registries. The United Kingdom–based Current Controlled Trials’ meta-register is an example of a registry that may compile the data from smaller registries. The World Health Organization (WHO) is working together with the ISRCTN and ClinicalTrials.gov to develop a common scheme to reduce duplicate registrations and publications and to establish the unambiguous identification of trials with the use of a unique numbering system. This is an important standard that must be met if registries are to be maximally effective.

But the WHO does not have the last word on this subject. For example, the Ottawa statement on trial registration goes much further than the WHO minimal data set. Its principles are to disclose the protocol details up front, to disclose amendments along the way, and to post the results at the end. The principles underlying this statement have been endorsed by more than 100 persons and organizations on all five continents, but not by a single pharmaceutical company.

This strategy is more than wishful thinking. The ultimate goal should be to make trial protocols publicly available in their entirety, including any financial arrangements and agreements with regard to publication, so that patients can be sure that the results will become available. At the same time, it is the responsibility of those who set the rules and establish the registries to make them practical to use and understandable for all kinds of research groups, both small and large. Only then will the use of registries become sufficiently comprehensive. The widespread use of trial registries will not prevent negative trial results or unwelcome outcomes from remaining unpublished. The current demand for the public registration of all clinical trials at their inception must therefore be followed by a demand for the addition of all results after each trial is complete and a certain amount of time has elapsed, to allow the researchers to publish in a journal.

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

From the Journal of the Norwegian Medical Association, Oslo (C.H.); the Nordic Cochrane Centre, Copenhagen (P.C.G.); and the Journal of the Danish Medical Association, Copenhagen (T.V.S.).


Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

We have recently obtained information regarding inaccuracies in data in the report of the VIGOR (Vioxx Gastrointestinal Outcomes Research) study by Bombardier et al.¹ that raise concern about certain conclusions in the article.

The VIGOR study was designed primarily to compare gastrointestinal events in patients with rheumatoid arthritis randomly assigned to treatment with rofecoxib (Vioxx) or naproxen (Naprosyn), but data on cardiovascular events were also monitored. Three myocardial infarctions, all in the rofecoxib group, were not included in the data submitted to the Journal. The editors first became aware of the additional myocardial infarctions in 2001 when updated data were made public by the Food and Drug Administration.

Until the end of November 2005, we believed that these were late events that were not known to the authors in time to be included in the article published in the Journal on November 23, 2000. It now appears, however, from a memorandum dated July 5, 2000, that was obtained by subpoena in the Vioxx litigation and made available to the Journal, that at least two of the authors knew about the three additional myocardial infarctions at least two weeks before the authors submitted the first of two revisions and 4½ months before publication of the article. Given this memorandum, it appears that there was ample time to include the data on these three additional infarctions in the article.

The fact that these three myocardial infarctions were not included made certain calculations and conclusions in the article incorrect. Although only summary percentages, not actual numbers of myocardial infarctions, were included in the Journal article, the following tables display the numerical data without (Table 1) and with (Table 2) the three myocardial infarctions.

Lack of inclusion of the three events resulted in an understatement of the difference in risk of myocardial infarction between the rofecoxib and naproxen groups (presented in the article as a reduction in the risk with naproxen but shown here as an increase in the risk with rofecoxib). It also resulted in the misleading conclusion that there was a difference in the risk of myocardial infarction between the aspirin indicated and aspirin not indicated groups.

Table 1. Data on Myocardial Infarctions Omitting the Three Events.¹

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Person-Years of Exposure</th>
<th>No. of Myocardial Infarctions</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2315</td>
<td>17</td>
<td>4.25</td>
<td>1.39 to 17.37</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2316</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>95</td>
<td>8</td>
<td>∞</td>
<td>1.65 to ∞</td>
</tr>
<tr>
<td>Naproxen</td>
<td>92</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin not indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2220</td>
<td>9</td>
<td>2.25</td>
<td>0.63 to 10.02</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2224</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ The numbers of person-years of exposure as of February 10, 2000, have been estimated. Relative risks were estimated by Poisson regression; confidence intervals were calculated by the exact method.

Table 2. Data on Myocardial Infarctions Including the Three Events.¹

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Person-Years of Exposure</th>
<th>No. of Myocardial Infarctions</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2698</td>
<td>20</td>
<td>5.00</td>
<td>1.68 to 20.13</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2699</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>105</td>
<td>8</td>
<td>∞</td>
<td>1.66 to ∞</td>
</tr>
<tr>
<td>Naproxen</td>
<td>102</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin not indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2593</td>
<td>12</td>
<td>3.00</td>
<td>0.91 to 12.78</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2597</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Relative risks were estimated by Poisson regression; confidence intervals were calculated by the exact method.
In addition, the memorandum of July 5, 2000, contained other data on cardiovascular adverse events that we believe would have been relevant to the article. We determined from a computer diskette that some of these data were deleted from the VIGOR manuscript two days before it was initially submitted to the Journal on May 18, 2000.

Taken together, these inaccuracies and deletions call into question the integrity of the data on adverse cardiovascular events in this article. We have asked the authors to submit a correction to the Journal.


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Autoantibodies in Prostate Cancer

TO THE EDITOR: Wang et al. (Sept. 22 issue)\(^1\) constructed a 22-phage-peptide detector for prostate cancer, with 81.6 percent sensitivity and 88.2 percent specificity. Previously, we constructed a decision tree for classifying prostate cancer, using five tumor-associated antigens, with 79 percent sensitivity and 86 percent specificity.\(^2\) With a smaller panel, these rates are equivalent to those of Wang et al. and might be improved by the selection of other tumor-associated antigens.

Only four peptides in the panel that was developed by Wang et al. were derived from in-frame coding sequences. Whether the other 18 peptides are mimotopes could be determined, for example, by analyzing the phage-peptide panel with other controls, including serum from patients with autoimmune disorders and other diseases. In our study and in other trials,\(^3\) known tumor-associated antigens were used in the antigen panels.

Nevertheless, the principal conclusion of Wang et al. — that their panel could provide a screening test for prostate cancer — is tenuous. Operating characteristics of the authors’ test, as well as of our panel of tumor-associated antigens, do not justify adoption in a screening program. Proportionately, too many cancers would be missed, and high false positive rates would be distressing. Evaluation of putative screening tests should include the calculation of likelihood ratios, as was previously advocated.\(^4\)

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TO THE EDITOR: Wang et al. report that autoantibodies against prostate cancer–specific peptides could be useful in a screening test for prostate cancer. However, their autoantibody screening system was positive for prostate cancer in 30 percent of patients with lung adenocarcinoma. Moreover, eukaryotic translation initiation factor 4 gamma 1 (eIF4G1), which was one of the new biomarkers used by Wang and colleagues, is overexpressed in 72 percent of cases of lung adenocarcinomas and is not a specific marker for prostate cancer.

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THIS WEEK’S LETTERS

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TO THE EDITOR: Wang and colleagues have not clarified whether their study controls were thoroughly investigated to rule out cancer so as to avoid any cross-reactivity. They do not mention the number of times reshuffling of their training and validation sets was done during the analysis; at least $59! + 70!$ different combinations of the training set can exist. Ein-Dor et al. have conclusively shown that repeating the analysis on several reshuffled training sets takes away the uniqueness of a molecular signature. They demonstrated that in 70 percent of such reshuffled training sets, more than one signature with equal or better predictive ability exists. Therefore, if this experiment is reanalyzed using a few hundred reshuffled training sets, there could be multiples of 22 autoantibody signatures with the same accuracy; these 22 autoantibodies could just be a few of many antibodies that are elevated in prostate and other cancers. We wonder if this is the real reason for an approximate 30 percent detection rate of this signature in patients after prostatectomy, in those with hormone-refractory prostate cancer, and, intriguingly, in those with lung cancer.

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TO THE EDITOR: Wang et al. propose a new marker for the diagnosis of prostate cancer. They studied a panel of peptides in a group of patients with biopsy-proven prostate cancer and in a group of men (defined as controls) without a history of prostate cancer. Nevertheless, the authors do not provide rigorous evidence of the absence of prostate cancer in the so-called control group. To avoid a verification bias, the authors should provide the results of end-of-study biopsies in the control group.

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THE AUTHORS REPLY: In response to Tan and Koziol: In the study by Koziol et al., which differs considerably from ours, seven tumor-associated antigens were arbitrarily selected and used in a multiplex enzyme-linked immunosorbent assay to monitor autoantibody levels in patients with cancer. In our study, we identified new peptides that are immunogenic in patients with prostate cancer, as compared with control subjects. The panel could be cut from 22 to 10 phage peptides with equivalent performance characteristics.

The assays in both trials had approximately 80 to 90 percent sensitivity and specificity for the detection of prostate cancer. The recursive partitioning algorithm used by Koziol et al. suffers from the limitation that the described trees are unstable (i.e., if the data are perturbed by the addition of stochastic noise, it will affect the variables and cutoff points chosen for the trees).

We agree that both approaches could be improved by the inclusion of additional tumor antigens and that neither method has yet achieved the performance characteristics or additional validation necessary for adoption in screening programs. Regarding the likelihood ratio, it is equivalent to the risk score we have developed by Bayes's theorem.

In response to Kida: Owing to the high prevalence of prostate cancer, a substantial fraction of the patients with lung adenocarcinoma, especially those 55 years of age or older, might very well be expected to have prostate cancer. Thus, some of the autoantibodies that were identified for prostate cancer may be shared by patients with lung cancer.

Although autoantibodies to eIF4G1 may not be specific to prostate cancer, in the context of a 22-peptide panel, they may be useful in detecting prostate cancer.

In response to Thorat and Badwe: The possible number of combinations of training and test sets is actually $(129! ÷ (70! × 59!)) × (128! ÷ (68! × 60!))$. The point of the randomization analysis is to determine whether the sensitivity and specificity of the optimal classifier change on the basis of the training and test sets used, not to determine the identity of the optimal classifier. Thorat and Badwe are confusing this issue with the issue of the uniqueness of the signature.

In response to Rocco et al.: We agree that a limitation of our study is that the control group did not undergo biopsy to confirm that they did not have incidental prostate cancer. That said, a
negative biopsy result does not completely rule out the presence of prostate cancer. In a follow-up prospective study, we are evaluating patients with negative biopsy results.

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Drs. Wang and Chinnaiyan report being listed as inventors on a patent on the findings of this study filed by the University of Michigan.


Prophylactic Thyroidectomy in Multiple Endocrine Neoplasia Type 2A

TO THE EDITOR: In their report on the effects of early prophylactic thyroidectomy in patients with multiple endocrine neoplasia type 2A (MEN-2A) (Sept. 15 issue),1 Skinner et al. identified a group of patients with postoperative calcitonin levels that increased in response to calcium–pentagastatin stimulation but remained within the normal range. The finding was regarded as presumptive evidence of persistent or recurrent medullary thyroid carcinoma. An alternative possibility that has not been ruled out is that there was production of calcitonin by extrathyroidal cells, particularly cells in the parathyroid glands or lung. Immunohistochemical detection of calcitonin in hyperplastic parathyroid tissue has been reported in two studies,2,3 one of which also involved the localization of calcitonin messenger RNA to the immunoreactive cells with the use of in situ hybridization.2 Immunoreactive calcitonin has also been reported in neonatal lung tissue.4 Both immunohistochemical analysis and in situ hybridization are methods fraught with potential artifacts, and the authors’ findings require replication by more specific techniques. Such confirmation would require modification of the postoperative assessment of pediatric patients who undergo thyroidectomy. It would also raise a number of interesting questions, including why extrathyroidal calcitonin-producing cells are not sites of origin for new primary medullary carcinomas in patients with MEN-2A.

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THE AUTHOR REPLIES: Dr. Tischler and colleagues and others whom they cite detected calcitonin with the use of immunohistochemical techniques in neonatal lung tissue or in hyperplastic or adenomatous parathyroid tissues (but not in normal parathyroid tissue). They propose that such extrathyroidal sources of calcitonin may account for the elevated plasma levels of this hormone that were detected postoperatively in some children in our study.
Although plausible, their proposal raises some concerns. Each of the three cited studies involved the use of immunohistochemical analysis of formalin-fixed and paraffin-embedded tissues. However, there were no functional studies to show that hyperfunctioning parathyroid cells or neonatal lung tissues actively secreted calcitonin into the bloodstream. Without such data, it is difficult to prove or disprove their hypothesis. We agree with the statement of Tischler et al. that immunohistochemical analysis and in situ hybridization are fraught with potential artifacts and require replication by more specific techniques. We would hope that data confirming that extrathyroidal sources of calcitonin either do or do not cause elevated blood levels of the hormone will be forthcoming in future studies.

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**TO THE EDITOR:** Nigro et al. (Sept. 29 issue) report on the administration of cytomegalovirus (CMV) hyperimmune globulin to 68 pregnant women with primary CMV infection and conclude that this treatment “may be effective in the treatment and prevention of congenital CMV infection.” However, 39 of 45 newborns with amniocentesis-proven congenital infection still shed virus at birth, and in utero infection was never documented in the remaining 84 newborns in the “prevention” group (in which women who had a recent primary infection before 21 weeks’ gestation or who declined amniocentesis were offered monthly hyperimmune globulin), only 37 of whose mothers received CMV hyperimmune globulin prenataally. Although amelioration of the severity of newborn disease was achieved, a claim of prevention of disease is not fully supported by the data.

We recently reported a case of successful clearance of in utero CMV infection in an immunosuppressed renal-transplant recipient whose CMV infection was reactivated during pregnancy. Serial amniocenteses confirmed initial fetal infection with subsequent clearance in conjunction with therapeutic levels of ganciclovir in the amniotic fluid. We propose that, just as antiviral agents specific to the human immunodeficiency virus (HIV) prevent vertical HIV transmission, CMV-specific antiviral therapies (including the preliminary findings of Nigro et al. regarding CMV immunoglobulin) be incorporated into future research protocols for preventing newborn CMV infection and illness.

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of viral load. The absence of a reduction in the rate of viremia in the group of women receiving the “prevention” treatment, in whom the time between maternal infection and hyperimmune globulin administration was shorter than in the “therapy group” (5 to 9 vs. 10 to 15 weeks), would not support the proposed “prevention” treatment.

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TO THE EDITOR: The possibility of significantly reducing the rate of intrauterine transmission of CMV and virtually abolishing the risk of congenital disease by the administration of CMV hyperimmune globulin to CMV-infected pregnant women, as reported by Nigro et al., sounds extraordinarily important. Unfortunately, the article does not provide evidence that this might be the case because it reports an uncontrolled study. Currently, women of childbearing age are neither informed about CMV nor tested for CMV antibodies. In addition, in the absence of screening during pregnancy, primary CMV infections in pregnant women are mostly undiagnosed, and no treatment is available for those with proven primary infection. In the context of such global indifference to the problem, the publication of an uncontrolled study claiming such impressive results is unhelpful. Pregnant women are a vulnerable group and deserve scientifically valid results. Investigators including Nigro and La Torre have already published similar data, and they should have confirmed their original results in a properly controlled study.

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THE AUTHORS REPLY: Silverman et al. confuse infection and disease, and they state that CMV hyperimmune globulin was expected to terminate viral excretion. That infected fetuses would remain infected after the administration of CMV hyperimmune globulin was anticipated, because viral excretion in infected newborns persists for years regardless of neutralizing antibodies. In our prevention group, the end point was not prevention of disease but prevention of infection, which occurred. In this group, a reasonable assumption was that the uninfected infants were never infected in utero. We did not determine whether the reduced infection rate was associated with lowered maternal or placental viral loads. Ganciclovir reduces viral loads, but CMV excretion resumes after cessation of the drug, so its efficacy may be similar to that of CMV hyperimmune globulin.

To Dr. Carbillon, the effect of the administration of CMV hyperimmune globulin was “amazing,” but it should not have been if hyperimmune globulin resolved fetal disease by neutralizing the virus and thus reducing placental inflammation and insufficiency, which would lead to improved fetal nutrition and oxygenation. This is plausible because most manifestations of congenital CMV infection resolve over the first weeks of life with improved nutrition and oxygenation. Our unpublished data suggest that placental size doubled throughout the second half of pregnancy among mothers with symptomatic fetuses, and the enlarged placentas decreased in size after the administration of CMV hyperimmune globulin to mothers with a primary CMV infection. Thus, one site of action of CMV hyperimmune globulin is probably the placenta, and the manifestations of congenital CMV at birth are probably caused in part by placental insufficiency.

All the newborns who had been treated with CMV hyperimmune globulin had birth weights appropriate for their gestational ages. Reduced maternal viral loads may be associated with the reduced rate of fetal infection in the prevention group. However, even if CMV hyperimmune globulin does not reduce maternal viral load, it may still prevent transmission of CMV to the fetus by reducing either placental viral load or inflammation.

In our prospective study, for ethical reasons, we were not permitted by the ethics review boards to assign controls randomly. Our multivariate
analyses, however, identified no selection bias, and they also indicated that treatment with CMV hyperimmune globulin was an independent predictor of fetal outcome. Furthermore, all relevant biologic data are consistent with our observations, which included the following findings: the CMV hyperimmune globulin contained high levels of neutralizing antibody; the rates of CMV transmission and disease that we observed were in line with those previously reported by others; preexisting maternal immunity is protective against CMV infection and disease; and in experiments in animals going back 25 years, passive immunization is effective. We encourage Dr. Revello and her colleagues to conduct confirmatory trials.

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Staphylococcal Sepsis in Children

TO THE EDITOR: The article by Adem and colleagues (Sept. 22 issue) described three patients with severe sepsis caused by *Staphylococcus aureus* who had, at autopsy, bilateral adrenal hemorrhage. Two of the patients had elevated serum cortisol levels. Is it possible that clinical deterioration was associated with a sudden decrease in the plasma cortisol level, which is expected after bilateral adrenal hemorrhage? In patients with severe sepsis, the use of corticosteroids may improve the clinical course. Current evidence suggests that corticosteroids improve outcome in adults for whom the results of a corticotropin stimulation test are abnormal (despite an elevated baseline cortisol level). Whether corticosteroids have this effect in children is unknown. The current clinical guidelines of the American College of Critical Care Medicine for the treatment of sepsis in children, and the pediatric considerations in the guidelines of the Surviving Sepsis Campaign, recommend the use of corticosteroids in children with purpura fulminans, as was seen in the cases reported by Adem et al. We would be interested to know whether corticosteroids were used in these patients, and if so, at what time in the disease course?

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THE AUTHORS REPLY: We agree with Drs. Branco and Tasker that preliminary data show that the early use of corticosteroids may improve the outcome in children with sepsis and bilateral adrenal hemorrhage. Patients 2 and 3 in our study did receive corticosteroids. Patient 2 was started on stress doses of hydrocortisone on the first evening after an arrest, and Patient 3 received dexamethasone in the emergency department and continued to receive corticosteroids during his brief hospitalization. Patient 1 did not receive corticosteroids. We have been initiating stress-dose corticosteroid therapy in children who have evidence of severe sepsis and hemodynamic instability, and we hope that additional data will help to determine definitively the merits of this approach.

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Chaperones and Disease

TO THE EDITOR: In Table 3 of their excellent review, Macario and Conway de Macario (Oct. 6 issue) state that an elevated level of circulating heat-shock protein (HSP) 70 has not been associated with any disease. However, we recently described elevated levels of circulating HSP70 in sickle cell disease. The increase in the level of HSP70 probably contributes to cytokine activation, since the protein may be released as a consequence of cell damage resulting from repeated episodes of ischemia–reperfusion injury.

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TO THE EDITOR: With regard to their insightful overview of the possible roles of aberrant molecular chaperones in disease states, Macario and Conway de Macario mention that an increase in neuronal expression of glucose-regulated protein 78 (Grp78), a member of the HSP70 family, is associated with Alzheimer’s disease. They also note that autoantibodies to specific chaperones may be correlated with certain disease states and cite an association of autoantibodies to HSP47 with autoimmune disease and autoantibodies to HSP60 and HSP70 with hearing loss. We would like to mention that autoantibodies to Grp78 are associated with metastatic androgen-independent prostate cancer. The origin of anti-Grp78 antibodies in prostate cancer is unclear but may involve the up-regulation of cell-surface expression of Grp78 on prostate-cancer cells.

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TO THE EDITOR: Macario and Conway de Macario omitted the connection between HSP90 and systemic lupus erythematosus. Levels of HSP90 are elevated in some patients with this disorder, especially those with neuropsychiatric and cardiorespiratory manifestations of the disease. Although HSP90 is an intracellular chaperone, it is expressed on the surface of mononuclear cells in patients with systemic lupus erythematosus who have a high level of disease activity. Autoantibodies against HSP90 were detected in a proportion of patients with systemic lupus erythematosus who have renal disease and a low C3 level.

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THE AUTHORS REPLY: In our short review, as noted by the correspondents, many publications could not be cited. Drs. Adewoye and McMahon say that we state in Table 3 of our article that an elevated level of circulating HSP70 has not been associated with any disease. What is actually meant in the row in our table pertaining to HSP70 (from data by Jin et al.) is that these authors found the...
chaperone in serum from healthy men. They re-
ported that HSP70 in serum was not associated
with any syndrome or disease in the persons they
studied. Other investigators have found HSP70 in
serum in association with pathologic conditions,
as Drs. Adewoye and McMahon have done. For
example, Njemini et al. reported that in elderly
people, HSP70 in serum was associated with in-
flammatory syndromes. Investigations should con-
tinue to elucidate why and by what mechanism
chaperones appear in biologic fluids and whether
these extracellular chaperones are initiators of
autoimmune pathogenesis or are useful disease
markers.

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of heat shock protein 70 in ageing: a study in the normal Chi-
2. Njemini R, Demanet C, Mets T. Inflammatory status as an
important determinant of heat shock protein 70 serum concen-

Table 1. Body-Mass Index and Metabolic Data Obtained before Laparoscopic Adjustable Gastric Banding and during Episodes of Hyperinsulinemic Hypoglycemia. 

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Before LAGB</th>
<th>During Episode of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI</td>
<td>At 120 Minutes during OGTT</td>
</tr>
<tr>
<td></td>
<td>mg/dl</td>
<td>serum glucose</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>115</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>153</td>
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<td>7†</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>263</td>
</tr>
</tbody>
</table>

* LAGB denotes laparoscopic adjustable gastric banding, OGTT oral glucose-tolerance test, and BMI body-mass index (the weight in kilo-
grams divided by the square of the height in meters).
† Patient 7 had two episodes of hyperinsulinemic hypoglycemia; all other patients had only one.

Asymptomatic Hyperinsulinemic Hypoglycemia after Gastric Banding

TO THE EDITOR: Service et al. (July 21 issue) recently reported on six patients with hyperinsul-
linemic hypoglycemia and nesidioblastosis after Roux-en-Y gastric bypass surgery. The authors
postulated that the rapid presentation of nutri-
ents in the duodenum stimulated excessive secre-
tion of glucagon-like peptide 1, leading to islet-
cell hypertrophy, proliferation, and neogenesis.

This report prompted us to review the incidence
of hyperinsulinemic hypoglycemia after laparo-
scopic adjustable gastric banding (LAGB), the
most common bariatric procedure performed in
Europe. This procedure effectively achieves gas-
tric restriction and a durable weight loss in obese
patients without permanently altering the intes-
tinal anatomy, improves insulin resistance, and
prevents the development of type 2 diabetes mellitus and hypertension.²⁻⁴

We followed 221 patients who underwent LAGB for morbid (grade III) obesity (according to the classification system of the World Health Organization) and measured serum levels of glucose and insulin at 0 minutes and 120 minutes after administration of 75 g of glucose before surgery and at 6, 12, 18, 24, and 36 months after surgery. No patient had hyperinsulinemic hypoglycemia (serum glucose level, <55 mg per deciliter; serum insulin level, ≥23 μU per milliliter) 120 minutes after the ingestion of glucose before LAGB. During follow-up (433 patient-years), we recorded nine episodes of asymptomatic hyperinsulinemic hypoglycemia in eight patients (five women and three men, 23 to 47 years of age, none of whom were receiving insulin or sulfonylureas at the time of the episode) (Table 1). All episodes were recorded 120 minutes after glucose ingestion, and six episodes occurred within one year after the patient had undergone LAGB. Assessment according to the homeostatic model (fasting insulin [μU per milliliter] × fasting glucose [mM per liter] ÷ 22.5) indicated a profound reduction in insulin resistance in all eight patients. In seven of them, no further episodes of asymptomatic hyperinsulinemic hypoglycemia occurred during the additional median follow-up period of 12 months (range, 12 to 30).

Our data show that transient asymptomatic hyperinsulinemic hypoglycemia occurs in 3 to 4 percent of patients after LAGB. We hypothesize that the substantial weight loss after this procedure markedly reduces insulin resistance in the context of beta-cell hypertrophy and hyperfunction that are commonly found in obesity.⁵ Further studies are needed to clarify the pathogenesis of transient hyperinsulinemic hypoglycemia after LAGB.

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AS WE APPROACH THE 25TH ANNIVERSARY of the first reports of the disease that would become known as AIDS, one might wonder what more there is to be written about the responses to the epidemic by Western nations. Much of the territory covered in Peter Baldwin’s Disease and Democracy is familiar, having been thoroughly documented in the vast academic and popular literature on the social, political, and cultural ramifications of AIDS. But the book has several strengths — above all, its comparative international perspective — that make it a fresh and enlightening contribution.

Baldwin, a historian who has analyzed the different approaches to illness, medicine, and politics in European countries, seeks to account in his current book for variations among Western nations in public health policymaking. He primarily concentrates on the United States, Britain, France, Germany, and Sweden, with occasional side trips to other European nations and industrialized countries in other regions. He examines each country’s policy responses in the context of its legal and constitutional systems, cultural beliefs and practices, demography, and even its physical geography and topography.

Baldwin advances two related arguments. First, he contends that the responses of industrialized nations differed in striking and often counterintuitive ways. All the countries he describes drew on a shared set of public health strategies: coercive interventions such as isolation of infectious patients, mandatory reporting of cases, and criminalization of transmission, and persuasive measures such as health education and promotional campaigns to prevent the spread of HIV and improve the health of those infected. Choosing among these approaches required confronting the perennial ethical and legal questions that arise when governments attempt to balance individual rights and communal well-being. The measures each country adopted, Baldwin shows, did not always map neatly onto its political or civic culture.

Second, he argues that patterns of history weighed heavily on the policy choices that were made and that national responses were influenced by precedents dating, in many instances, to encounters with disease in the 19th century. Baldwin repeatedly invokes the military metaphor of generals fighting the previous war, with each country’s public health leaders falling back on approaches tested against earlier contagions, such as smallpox and cholera.

Baldwin takes for granted that his audience has a fair amount of knowledge about the countries under analysis, and it may at times be heavy going for readers not well versed in the varied political and social contexts within which AIDS policymaking took place. The material is organized thematically, with chapters devoted to issues such as legal discrimination, questions of individual responsibility and voluntarism, the influence of patient advocacy groups, and the contested status of scientific authority. This structure is effective for placing divergences in policy into sharp relief but is less effective for presenting a coherent picture of any one country.

Nevertheless, Baldwin has synthesized an impressive amount of material with skill and nuance. He is skeptical toward cant and conventional wisdom; the chapter on identity politics and the effects of activism by interest groups regarding measures to prevent AIDS is especially incisive. Baldwin’s lively and sardonic writing style is refreshingly unacademic (though his colorful turns of phrase sometimes cloy). Disease and Democracy illustrates how valuable a historical and cross-national framework can be for understanding the contentious process of public health policymaking.

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global health leadership
and management


It is a welcome breath of fresh air to read William H. Foege’s preface to Global Health Leadership and Management. He zeroes in on the looming crisis in global public health with a tiger’s instinct for the jugular vein.

Bridging the huge gap between the knowledge of medical science and the delivery of public health is the focus of this book. From the standpoint of global public health, medical science that goes undelivered is the same as no medical science at all. To Foege, the effective and sustainable delivery of medical science is critical to achieving better world health. He believes that the key is creative and effective leadership and management.

Foege declares that science is not enough, good intentions do not change the health picture, and resources are easily wasted. We need the same constant attention that is absolutely expected in the business community, with a focus on developing objectives, working out strategies for reaching those objectives, organizing all components of a program to pursue the strategy, pushing for continuous quality improvement, and developing the ability to measure both process and outcome goals for constant midcourse corrections.

He goes on to state that “global health waits expectantly for management to match its science” (and, I might add, for more leaders and commentators who can match Foege’s insight and vision). With that, the powerfully written preface ends.

What follows, in a well-organized fashion, is a collection of 17 essays of varying quality, each 6 to 18 pages in length, written by some of the most prominent figures in international public health. A few of the contributors merely restate the problem or recite the obvious and do not build particularly well on Foege’s excellent foundation — perhaps understandably, because this book charts truly new territory. It must have been difficult to organize such an army of prominent explorers and to keep them marching in the same direction. Editing the book must have been a considerable challenge. Overall, however, it has come out well. The occasional and probably unavoidable unevenness does not really matter, because many contributors have delivered pure diamonds. These essays alone are well worth the price of the book and the time it takes to read it.

Harlan Cleveland’s essay regarding the broad effects that the global information revolution may be having on global public health is particularly thoughtful, as well as thought-provoking. Nils Daulaire presents a powerful analysis of the striking similarities between the characteristics of successful leaders at the local level in global health and those of managers at the level of individual business enterprises. Susan Dentzer details the important lessons to be taken from Brazil’s approach to HIV and AIDS. Jo Ivey Boufford effectively addresses the critical problem of how to find, train, retain, and motivate the extraordinary people who will be the agents and leaders of change. She examines this problem from the standpoint of what has worked well in the business world.

When I began reading the short contribution from Jeffrey D. Sachs, I was prepared to be disappointed with a brief summary of what he has often expressed before — how could he present anything really new in only six pages? I was wrong. The last half of his essay should be published in the opinion and editorial pages of major newspapers everywhere. It is a precise, four-step blueprint for poor countries to obtain more financing for health services from donors. It is also a practical and politically savvy prescription that incorporates the best of business planning and management.

This collection does not (and as structured, obviously could not) address in depth many of the obstacles of structure, politics, and values that confront global public health. But it does offer important new ideas and ways of thinking that will be essential to incorporate if substantial progress is to be made. In that respect, it is a must-read for anyone who has a stake in global public health, which means everyone.

A particular challenge is that many of the changes that are needed could be perceived to threaten the niches of global health professionals. The changes will need to be spearheaded by “transformational leaders” in the field, as Cleveland refers to them. As he says, “It takes an unusual measure of both self-confidence and tact for...
Perspectives on Health and Human Rights

During the past decade, a growing body of interdisciplinary academic literature has explored the relationship between health and human rights. Not surprisingly, much of that scholarship has focused on either the health implications of human rights violations or the effect of health policies and programs on human rights. Another dominant theme is the synergy between health and human rights. Contributors have sought to substantiate the hypothesis of the late Jonathan Mann that the promotion and protection of health and human rights are “inextricably linked.” A selection of articles in this new field was reprinted in Health and Human Rights: A Reader, edited by Mann et al. (New York: Routledge, 1999), and this book soon became a popular teaching aid at schools of public health offering courses on health and human rights. Perspectives on Health and Human Rights is described as a “follow-up” and companion volume to this earlier collection.

Like its predecessor, Perspectives reproduces already published work. It opens with a broad analysis of the links between health and human rights. (For those unfamiliar with the field — and, in particular, with human rights treaties, law, and institutions — the first chapter is a useful primer.) Articles exploring these links are then arranged into four substantive sections: development, emerging technologies, sexual and reproductive health, and violence. Although these categories provide a helpful framework, they are necessarily broadly construed and tend to lead to some unusual bedfellows. The section on emerging technologies begins with two articles on cloning and genetic manipulation, before drawing attention to less glamorous but far more important work on patents and access to essential drugs. In the section on violence, a persuasive article by Joan LeGraw and Michael Grodin condemning the participation of medical personnel in executions by lethal injection rubs shoulders with a report by Physicians for Human Rights on maternal mortality in the Herat Province of Afghanistan.

Two subsequent sections explore the use of qualitative and quantitative methods in health and human rights and analyze recent case law from South Africa and Venezuela on the “right to health” — a concept alien to U.S. jurisprudence. The book ends with a discussion of human rights advocacy, education, and mobilization that makes clear the editors’ commitment to health and human rights as something more than an intellectual discipline. The editors emphasize the responsibility of health professionals to protect and promote human rights, and one editor observes that “medical ethics devoid of human rights become no more than hollow symbols.” This is all the more poignant in light of the recent revelations concerning the role of health care personnel in aggressive interrogations at Abu Ghraib and Guantanamo Bay.

It is easy to criticize collections for errors of omission, but there is a conspicuous absence here. Although the events of September 11, 2001, and the severe acute respiratory syndrome epidemic of 2003 are mentioned briefly in the introduction, none of the chapters in the book focus on the tensions between the protection of human rights and public health in the context of public health emergencies, whether due to terrorism or acts of God. The significance of these issues has been highlighted by Hurricane Katrina (and its aftermath) and by the emergence of avian flu as a global threat, but important developments and debates in both domestic and international arenas predate these occurrences.

That said, Perspectives on Health and Human Rights is a handy compendium of some of the recent literature. It will also be a valuable teaching aid for anyone seeking to bring health and human rights into the curriculum of a school of public health, law, medicine, or nursing.

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Perspectives on Health and Human Rights
NOTICES

CORRECTIONS

Peritoneal Dialysis and Epithelial-to-Mesenchymal Transition of Mesothelial Cells (January 30, 2003;348:403-13). On page 408, Panel H of Figure 3 contains several errors. The corrected version of this figure appears with the full text of the article at www.nejm.org.

Case 25-2005: A 40-Year-Old Man with Prolonged Fever and Weight Loss (August 18, 2005;353:713-22). On page 714, lines 4 through 6 of the right-hand column should have read, “Pathological examination of the appendix was reported to show inflammation and no cancer,” rather than “. . . inflammation and cancer,” as printed. We regret the error.

Chronic Insomnia (August 25, 2005;353:803-10). On page 806, in Table 3, under the column heading Contraindications or Drug Interactions, all five listings should have read, “Drugs that inhibit CYP3A4” or “CYP1A2,” rather than “Drugs that induce CYP3A4” or “CYP1A2,” as printed.

Psoriasis (August 25, 2005;353:848-50). On page 848, lines 8 and 9 of the letter by Khan should have read: “. . . and in humans, these cells express the forkhead transcription factor FOXP3,” rather than “FOX33,” as printed. We regret the error.

Direct Thrombin Inhibitors (September 8, 2005;353:1028-40). On page 1029, in Figure 1, the arrow pointing from activated protein C and protein S to factors IXa and VIIIa should have been dashed (indicating an inhibitory pathway), rather than solid (indicating an activation pathway). Also, a dashed-line arrow should have been pointing from activated protein C and protein S to factors Xa and Va, rather than the reverse, as printed. These corrections to the figure appear with the full text of the article at www.nejm.org.

NOTICES

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

AMERICAN HEADACHE SOCIETY

The following meetings will be held: “2006 Winter Headache Symposium” (Henderson, Nev., Jan 27-29); “48th Annual Scientific Meeting” (Los Angeles, Feb. 27-March 3); “Principles of Epidemiologic Data Analysis/EP15” (Lunteren, the Netherlands, Feb. 27-March 3); “Psychiatric Epidemiology/EP12” (Utrecht, the Netherlands, April 10-13); “Clinical Trials and Drug Risk Assessment/CE04” (Utrecht, the Netherlands, April 24-28); “Planning and Evaluation of Screening/HS05” (May 8-12); “Cancer Epidemiology/EP13” (Amsterdam, May 15-19); and “Operational Research Applied to Health Services/HS07” (May 17-19).

SOUL SPEAK: PLAIN TALK ABOUT HEALTH LITERACY AND THE PHYSICIAN-PATIENT PARTNERSHIP

The conference will be held in Jackson Hole, Wyo., Feb. 8–11. It is presented by the University of Tennessee Graduate School of Medicine and College of Medicine.

Contact the University of Tennessee Graduate School of Medicine, 1924 Alcoa Highway, D-116, Knoxville, TN 37920-6999; or call (865) 544-9190; or e-mail afjohnso@ucvm.utk.edu; or see http://www.tennessee.edu/cme/healthliteracy.

HIGHLIGHTS OF ASH 2005

The annual meeting of the American Society of Hematology will be held in Miami, Feb. 10 and 11.

Contact the American Society of Hematology, 1900 M. St., Suite 200, Washington, DC, 22233; or call (202) 776-0944; or see http://www.hematology.org/meetings/highlights/index.cfm; or e-mail cme@hematology.org.

NETHERLANDS INSTITUTE FOR HEALTH SCIENCES

The following courses will be offered in Rotterdam, the Netherlands, unless otherwise indicated: “Epidemiology of Infectious Diseases/CE05” (Amsterdam, Feb. 13-17); “Advanced Diagnostic Research/CE10” (Utrecht, the Netherlands, Feb. 27-March 3); “Principles of Epidemiologic Data Analysis/EP15” (Lunteren, the Netherlands, Feb. 27-March 3); “Quantitative Models for Evaluation of Tropical Disease Control/HS06” (March 6-10); “Bayesian Statistics/CE09” (March 13-15); “Addiction and Substance Use/HS13” (March 20-24); “Medical Demography/HS04” (April 3-7); “Prognostic Research/CE11” (Utrecht, the Netherlands, April 3-7); “Psychiatric Epidemiology/EP12” (Groningen, the Netherlands, April 10-13); “Clinical Trials and Drug Risk Assessment/CE04” (Utrecht, the Netherlands, April 24-28); “Planning and Evaluation of Screening/HS05” (May 8-12); “Cancer Epidemiology/EP13” (Amsterdam, May 15-19); and “Operational Research Applied to Health Services/HS07” (May 17-19).

Contact the Netherlands Institute for Health Sciences, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands; or call (31) 10 408 8149; or e-mail info@nihes.nl; or see http://www.nihes.nl.

DIAMOND HEADACHE CLINIC

The following meetings will be held: “19th Annual Practicing Physician’s Approach to the Difficult Headache Patient” (Rancho Mirage, Calif., Feb. 14-18); “The National Headache Foundation’s Third Annual Headache Research Summit” (Rancho Mirage, Calif., Feb. 15 and 16); and “Headache Update 2006” (Lake Buena Vista, Fla., July 11-15). The meetings are jointly sponsored by the Diamond Headache Clinic Research and Educational Foundation, the Diamond Inpatient Headache Unit at Thorek Memorial Hospital, and Rosalind Franklin University of Medicine and Science.

Contact Diamond Headache Clinic Research and Educational Foundation, 467 W. Deming Place, Chicago, IL 60614; or call (877) 706-6363 (national) or (773) 388-6363 (Illinois); or fax (773) 477-9712; or e-mail info@dhc-fdn.org; or see http://www.dhc-fdn.org.

CLEVELAND CLINIC

The following courses will be offered in Cleveland: “5-Day Gamma Knife Radiosurgery Training Course” (Feb. 20–24, April 3–7, Aug. 21–25, Oct. 23–27, Dec. 4–8); “2nd Annual Pituitary Update Conference” (March 10); “Heart-Brain Summit” (June 16 and 17); and “Spine Review Hands-On 2006: A Comprehensive Approach for Neurosurgeons and Orthopaedic Surgeons” (July 19–25).

Contact The Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195; or call (800) 223-2273, extension 47591; or fax (216) 445-9999; or e-mail tobinnm@ccf.org; or see http://www.clevelandclinic.org/neuroscience/professionals/cme.
A 73-YEAR-OLD INUIT WOMAN WAS REFERRED FOR A BARIUM ENEMA AFTER AN INCOMPLETE COLONOSCOPY. A preliminary abdominal radiograph showed that the appendix was completely full of lead shot, with the contour of the appendix easily visualized. The natives of northern and western Alaska hunt waterfowl in the spring and fall and often inadvertently swallow some of the lead shot embedded in the meat. Although most of the metal undoubtedly passes through the intestine over time, buckshot in the appendix is commonly seen in Alaskan natives (but usually not to the extent pictured here). Decades of ingestion probably resulted in this large accumulation. It is likely that poor dentition and advanced age are aggravating factors that prevent detection of the lead during mastication. A round piece of buckshot can be seen on the patient’s right above the appendix — probably evidence of a recent meal.

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