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Anchors Away

Improving Global Health — Margaret Chan at the WHO
China and HIV — A Window of Opportunity
Bates Gill, Ph.D., and Susan Okie, M.D.

Last December in Wuhan, China, two middle-aged rural women who had become infected with HIV in the 1990s struggled to describe to foreign visitors how China’s new HIV-treatment program had changed their lives. Suddenly, one woman’s 12-year-old daughter spoke up. Her mother, she said, had been too sick to get out of bed, and the girl had left school to help at home and on the farm. But when the woman began taking antiretroviral drugs, she improved quickly, returned to work in the fields, and sent her daughter back to the classroom.

Such stories are increasingly common in China, reflecting a striking shift in the government’s approach to HIV. Although China’s first AIDS cases were discovered in 1989, the government did not publicly acknowledge the existence of a major epidemic until 2001. Two years later, as international attention mounted after the outbreak of severe acute respiratory syndrome (SARS), the government abruptly changed course, launching aggressive measures against AIDS. An interagency committee was created to coordinate a government-wide response, and a national AIDS treatment program was established. The national budget for HIV–AIDS grew from approximately $12.5 million in 2002 to about $100 million in 2005 and about $185 million in 2006. In January 2006, the Chinese Cabinet issued regulations for HIV–AIDS prevention and control, outlining the responsibilities of the central and local governments and stipulating the rights and responsibilities of infected persons. The law requires county-level jurisdic-

The government also announced a 5-year plan that sets ambitious targets for educating the public about HIV, reducing stigma, training health care workers and technicians, ramping up treatment, improving surveillance, and delivering counseling and interventions to at-risk populations. The government estimates that 650,000 Chinese people are infected with HIV and hopes to limit the total to 1.5 million by 2010.

“There’s really been a sea change” in China’s response, said Peter Piot, executive director of the Joint United Nations Program
Chinese and international health officials express optimism about controlling the epidemic but emphasize the need to move quickly. The current estimate represents an HIV prevalence of approximately 0.05% of the general population, but by the end of October 2006, only 183,733 infected persons had been identified, according to the Ministry of Health. Although HIV has been reported in all 31 Chinese provinces, about three quarters of infected persons are believed to reside in 5 provinces: Guangdong, Guangxi, Henan, Xinjiang, and Yunnan. Henan, along with several neighboring provinces in central China, was the site of a 1990s HIV outbreak among rural residents who became infected through contaminated equipment at commercial plasma-donation centers. The other four are border provinces, crisscrossed by heroin-trafficking routes, where HIV transmission is fueled by injection-drug use. The epidemic is “quite young,” said Ray Yip, director of the Chinese office of the U.S. Centers for Disease Control and Prevention (CDC), “It’s still concentrated very highly among the highest-risk group of people. It hasn’t really gotten out of hand even among the sex-worker population.”

But the situation could worsen rapidly. Among new HIV infections in China, 48.6% are caused by drug use, 49.8% by sexual transmission, and 1.6% by mother-to-child transmission, according to Connie Osborne, senior adviser to the World Health Organization (WHO) on HIV–AIDS care and treatment in Beijing. The country is undergoing rapid economic and social change, including migration from rural areas to cities and increases in prostitution and illegal drug use. “It’s a free-for-all kind of place,” said Yip. “If you don’t control the epidemic in the next 5 years . . . the sheer increasing numbers of people who engage in high-risk behavior can fuel the fire.” Given China’s enormous population, even a small increase in prevalence could be devastating. “If it went up to 4%, we would have 52 million infected, more than the total global figure today,” said Wu Zunyou, director of China’s National Center for AIDS/STD Control and Prevention (NCAIDS).

China’s determination to confront its epidemic has attracted major funding. As of late 2005, international assistance programs for HIV–AIDS had been implemented in 27 provinces, with contributions of approximately $229 million. China has received approximately $134 million for HIV programs from the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which will provide more than $14 million over the next 5 years to strengthen civil society organizations that can reach high-risk populations. China also receives aid for HIV–AIDS control from numerous other international partners.

In Beijing, it is common to hear health officials declare that controlling HIV–AIDS is now simply a technical matter of implementing existing policies. Although the Chinese government has indeed made some tough choices — for example, supporting needle-exchange programs and setting up methadone-maintenance therapy sites for injection-drug users — other critical problems must still be addressed.

First, those who are HIV-positive or in high-risk groups still bear a stigma and experience discrimination, both of which are major obstacles to care. Health care workers have been known to refuse to treat persons suspected of having HIV. People from “HIV villages,” such as those in Henan, where many plasma donors became infected, cannot find jobs, and agricultural produce from these locales cannot find markets.

Far greater stigma is attached to persons who contract HIV on HIV/AIDS (UNAIDS). “The central leadership and policies are nearly as good as they can be.”
through behavior that is criminal or deemed immoral. Injection-drug users and commercial sex workers, who make up the largest population of HIV-positive persons, are also among the most difficult to reach with counseling and treatment, in part because stigma drives them underground. There is tension between public health authorities, responsible for preventing and treating HIV infection, and public security officials, responsible for punishing illegal activity. Although officials in leadership positions may acknowledge that injection-drug users are patients as well as criminals, says Piot of UNAIDS, this understanding “has not been internalized by every policeman and security person.” The February 2007 detention of Gao Yaojie — an elderly doctor turned HIV–AIDS activist in Henan province — to prevent her from receiving an international award in the United States is just one recent case in which local authorities took action that was contrary to national policies. After international pressure was exerted, Gao was permitted to travel.

About half of China’s HIV-positive population contracted the virus by sharing needles for drug use. In 2005, the government authorized the rapid establishment of methadone-maintenance therapy sites throughout the country. According to Wu of NCAIDS, by the end of 2006, China had opened 320 such clinics, each dispensing methadone to an average of 200 patients per day; the aim is to have 1500 clinics operating by 2008. Yip of the CDC believes this program offers the strongest evidence of the government’s determination

**Cumulative Cases of HIV Infection in China, According to Province, as of December 2005.**

Data are from the Chinese Ministry of Health.
to stem the epidemic: “It signals that they understand the critical link between drug use and control of HIV–AIDS. It’s a permission to engage the most marginalized people.”

Currently, however, most sites do not offer more comprehensive services, such as needle and syringe exchange, peer counseling, testing, or employment counseling. In addition, the efforts of local authorities to set up such clinics are often met with resistance, ranging from complaints that the clinics attract “the wrong elements” to questions about why drug addicts should receive free or subsidized medical care when the average citizen does not. Although China has also implemented needle-exchange programs, Wu said that because these programs do not reduce injection-drug use, they will “only be used in places where methadone maintenance is not available.”

Men who have sex with men are another at-risk population that until recently received little attention. There are strong taboos against homosexual behavior in China, where men are under enormous pressure to marry and produce male heirs. Estimates of the population of men who have sex with men range from 5 million to 10 million, and the number may well increase as social mores continue to change. Chinese health officials estimate that nationwide about 1% of men who have sex with men are HIV-positive. They have established an advisory group including activists and behavioral specialists to formulate policies designed to reach this marginalized population, but China still has a long way to go in allowing nongovernmental and civil society organizations to contribute to the fight against HIV–AIDS.

China also faces the daunting task of locating the half-million or more people believed to be infected with HIV infection without knowing it. A massive testing program undertaken from 2004 through 2005 focused on identifying plasma donors infected during the 1990s outbreak and on conducting testing in drug-detoxification detention centers and prisons. This effort is the single largest factor in the recent dramatic increase in reported HIV–AIDS cases.

Still, an estimated 70% of infected persons remain unidentified. Outside the prison and drug-detoxification systems, HIV testing is voluntary. Mandatory premarital testing for sexually transmitted diseases was eliminated in October 2003, although some localities may reinstate it. Because of stigma, distrust regarding confidentiality, and the absence of effective counseling and referrals, most people are reluctant to be tested. Moreover, although screening tests are available free, patients usually must pay for confirmatory tests that cost $25 to $40 — nearly a month’s salary in parts of China. Reliance on confirmatory testing also increases loss to follow-up: many people never receive their results, according to Osborne, who says the WHO is promoting rapid testing.

China’s epidemic, unlike that in most countries, is concentrated in rural areas, where poor residents have little access to health care. The hard work of stemming the epidemic will fall to county-level jurisdictions. With more than 3000 counties in China, the task of ensuring an effective and relatively standard response will be an enormous one. The implementation of the central government’s mandates will vary widely, depending on local resources and priorities. HIV has hit hardest in the poorest, most remote areas that are hard-pressed to provide the money, training, and personnel needed. “With the introduction of the market economy, there has been a collapse of public health services and other services for the poor . . . particularly in rural areas,” said Piot of UNAIDS.
Getting treatment to people is therefore not so easy, even if the will is there. Since 2003, China has rapidly expanded the availability of first-line antiretroviral treatment. By the end of 2006, approximately 24,400 people were receiving therapy, up from about 20,450 in 2005, and the number is expected to reach 30,000 to 35,000 this year. But further increases are likely to be slower, since reaching marginalized groups will be more difficult than enrolling people infected through plasma donation. WHO authorities in Beijing fear that China’s treatment program may not reach its goal of extending free treatment to 80% of those who need it by 2010. With 1 million to 1.5 million expected to be HIV-positive by then, 200,000 or more people may require treatment.

Relying almost entirely on generic drugs produced in China, the country’s first-line therapy regimens — zidovudine, didanosine, and nevirapine or zidovudine, stavudine, and nevirapine — have severe side effects, raising concerns about adherence and the emergence of drug resistance. Laboratory tests to monitor treatment are not paid for by the central government, and the costs are commonly passed along to patients. In early 2005, more effective and less toxic compounds such as efavirenz and lamivudine became available and were introduced into some first-line regimens. Chinese health authorities are negotiating with foreign pharmaceutical firms to purchase second-line drugs, which are not widely available.

In addition, despite some new training programs, most regions lack health care providers with sufficient expertise to properly diagnose and treat AIDS and to monitor patients’ viral loads. With suboptimal treatment, drug-resistant virus will surely emerge, but a national drug-resistance surveillance system does not yet exist. The rate of resistance to first-line treatment was 18% in one small Chinese study but 45 to 80% in separate cohorts in another study. International health experts remain cautiously hopeful about China’s chances of controlling its epidemic. Success, however, will depend on how well the government handles challenges such as overcoming stigma, mounting aggressive outreach efforts for high-risk groups, and mobilizing funding, expertise, and commitment throughout the vast and diverse country to identify, counsel, and care for the people who are infected. Although a political corner has been turned in Beijing, there is still an enormous amount of work to be done on the ground.

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“When you have a country where the prevalence of HIV is less than 1 per 1000 and the government has started to respond seriously, that’s good news,” noted Yip of the CDC, but China must now implement strategies aimed at the hardest-hit populations. “A good policy,” he warns, “doesn’t always translate into a sound program.”

Dr. Gill reports receiving consulting fees from Merck and Abbott Laboratories and grant support from Merck and the Gates Foundation.

Dr. Gill is a China scholar at the Center for Strategic and International Studies, Washington, DC. Dr. Okie is a contributing editor of the Journal.
Subjects or Objects? Prisoners and Human Experimentation
Barron H. Lerner, M.D., Ph.D.

During the 1950s, inmates at what was then called Holmesburg Prison, in Philadelphia, were inoculated with condyloma acuminatum, cutaneous moniliasis, and viruses causing warts, herpes simplex, and herpes zoster. For participating in this research, and in studies exposing them to dioxin and agents of chemical warfare, they were paid up to $1,500 a month. Between 1963 and 1971, researchers in Oregon and Washington irradiated and repeatedly took biopsy specimens from the testicles of healthy prisoners; the men subsequently reported rashes, peeling, and blisters on the scrotum as well as sexual difficulties. Hundreds of such experiments induced the federal government to essentially ban research involving prisoners in 1978. The message: such research is fundamentally exploitative and thus unethical.

Yet a recent report by the Institute of Medicine (IOM) has opened the closed door, arguing not only that such research can be performed appropriately but that prisoners deserve to be included in investigative studies — at least those who might benefit directly. Examination of the explanations behind U.S. restrictions on prison research and their current applicability can provide guidance for today’s policy debates.

The vulnerability of prisoners to exploitation has long been known. As early as 1906, for instance, critics noted how difficult it would have been for prisoners to refuse to participate in a cholera experiment that ultimately killed 13 men. Still, investigators periodically sought out “volunteers” among such captive populations, whose institutionalization offered researchers accessible subjects unlikely to be lost to follow-up.

Most such research did not seek to benefit participants. In 1915, for example, Public Health Service researcher Joseph Goldberger induced pellagra in healthy Mississippi prisoners, who were offered parole in exchange for participation. Those who signed up experienced the very severe symptoms of the disease, including diarrhea, rash, and mental confusion. Goldberger, however, proved his hypothesis that pellagra was a vitamin-deficiency disease that could be cured by ingestion of the B vitamin now known as niacin. Thanks to this work, as well as the discovery of insulin and the first antimicrobial agents, the years between World War I and World War II were heady times for scientific research.

World War II turned questionable experimentation on prisoners into a cottage industry. As other Americans risked their lives on the battlefield, prisoners did their part by participating in studies that exposed them to gonorrhea, gas gangrene, dengue fever, and malaria. Any consideration of meaningful consent was subsumed by the war imperative.

Ironically, the biggest boost to such experimentation came as a result of the postwar Nuremberg trial of 20 Nazi doctors, which gave rise to the Nuremberg Code, a set of principles intended to prohibit human experimentation without subjects’ consent. When defense lawyers implied that American scientists had conducted wartime research analogous to that of the Nazis, one prosecution witness, Andrew C. Ivy, cited malaria experiments involving Illinois prisoners as an example of “ideal,” noncoercive research. Ivy’s 1948 publication of his conclusions helped to institutionalize prison experimentation for the next quarter-century.

It was an experiment involving another vulnerable population that halted the prison research enterprise. In 1972, an Associated Press reporter broke the story that poor southern black men with syphilis had been deliberately left untreated for 40 years so researchers could study the natural course of the disease. In the environment created by the civil rights movement and protests against the Vietnam War, such research was condemned. The scandal led to the formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and eventually the Belmont Report, which recommended revamping human experimentation using the principles of respect for persons, nonmaleficence, and justice.

In the case of prison research, the new atmosphere proved especially restrictive. In 1978, the Department of Health and Human Services (DHHS) passed regulations that limited federally funded research involving prisoners in several ways, stipulating, for example, that experiments could pose no more than minimal risk.
to the subjects. The overarching concern was that prisons were inherently coercive environments in which informed consent could never be obtained. The fact that research offered financial rewards, alleviation of boredom, and the prospect of earlier parole made it even more dicey.

This was the prevailing view until 2004, when the DHHS asked the IOM to revisit the matter. In August 2006 the IOM published its report, which acknowledged that it might make sense to leave the situation alone. For example, the U.S. prison population includes disproportionate numbers of vulnerable people: members of minority groups, the mentally ill, and persons with HIV infection and other serious infectious diseases. Prisons are generally overcrowded and have inadequate health care services. All these factors suggested that any easing of restrictions might lead to the repetition of previous errors.

Nonetheless, the IOM panel, although sensitive to past “unconsciousable abuses,” recommended that experiments carrying more than minimal risk be allowed, with the caveat that studies involving drugs or other biomedical interventions be required to have potential benefits for prisoners. The panel also recommended several safeguards, such as creating a public database of prison experiments, limiting research to interventions with some demonstrated safety and efficacy, ensuring that studies include a majority of nonprisoner subjects, and requiring that proposals be vetted by institutional review boards that would include prisoner representatives.

The panel’s decision makes sense for several reasons. The first might be termed historical. For most of the 20th century, despite the findings at Nuremberg and occasional other warnings, human experimentation was largely seen as a “good,” something that would advance science and benefit health. The backlash against experimentation in prisons occurred during the 1970s, when authority was being questioned throughout society. No mechanisms were in place to ensure the rights of vulnerable subjects. It thus made sense to ban any risky research in prisons.

It is often said that those who ignore history are condemned to repeat it. But a decision to retain current restrictions because of past abuses would ignore several important developments. Since 1978, a network of institutional review boards has been established at the National Institutes of Health, other governmental agencies, and research universities throughout the country. With “informed consent” now common parlance, study subjects are more aware of their rights. And, largely owing to the work of AIDS activists and breast cancer activists, sick and at-risk persons, even those from potentially vulnerable populations, now actively pursue participation in research protocols. Even though not all these developments are unambiguously positive, to ignore them and the opportunities they may afford prisoners would be to regress. As the IOM report said, “respect for prisoners also requires recognition of their autonomy.”

Another argument in favor of relaxing restrictions is that the reflexive assumption that all prison research is problematic may not be accurate. In light of the abuses, critics have understandably argued that human experimentation in prison has failed because it takes place in a coercive environment that vitiates any possibility of informed consent. But that is a theory that can and should be investigated empirically through formal studies of the consent process in prisons. Moreover, as philosopher Carl Cohen has argued, research outside of prisons often has coercive elements as well — so to the degree that coercion is involved, it may have little to do with imprisonment.

Finally, reinstating and then monitoring prison research would afford society an opportunity for ongoing scrutiny and reassessment. Indeed, the IOM panel found that much unregulated prison research was being conducted despite the 1978 guidelines. Many of the notorious prison experiments involved the active deception of study participants — an abuse more easily avoided if the whole enterprise is underground. It is even possible that research studies, by providing a window into prison life, would focus needed attention on deficiencies in prison health care.

Still, the new regulations must be approached with trepidation. As sociologist Erving Goffman showed in his 1961 book Asylums, “total institutions” such as prisons may run roughshod over the rights of their inhabitants. Perhaps this book should be required reading for any investigator who embarks on research within prison walls.

Dr. Lerner is an associate professor of medicine and public health at Columbia University, New York.

1. Hornblum AM. They were cheap and available: prisoners as research subjects in twentieth century America. BMJ 1997;315:1437-41.

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Once-Yearly Zoledronic Acid for Postmenopausal Osteoporosis

In this double-blind, placebo-controlled trial, women with postmenopausal osteoporosis received an infusion of either zoledronic acid (5 mg) or placebo at baseline and at 1 and 2 years and were followed for 3 years. Zoledronic acid significantly reduced the risk of vertebral, hip, and other fractures. Adverse events were similar in the two study groups, except for serious atrial fibrillation, which was more frequent in the zoledronic acid group. This drug may provide a promising approach to reducing fracture risk.

See P. 1809; Editorial, P. 1878; CME, P. 1902

Streptokinase Immediately after Primary Percutaneous Coronary Intervention

In this pilot trial, patients undergoing primary percutaneous coronary intervention were randomly assigned to receive a low dose of intracoronary streptokinase after reperfusion or no additional therapy. At 2 days, microvascular function was significantly improved in the streptokinase group. There was no significant difference in left ventricular size or function at 6 months, although the findings suggest that a larger trial might show such a benefit.

See P. 1823; Editorial, P. 1880; CME, P. 1903

Age at Surgery for Undescended Testis and Risk of Testicular Cancer

In a study of almost 17,000 men who were surgically treated for undescended testis, with data culled from Swedish national registries, the risk of testicular cancer among men who underwent orchiopexy at 13 years of age or older was twice that among men who had surgery before the age of 13. Surgical treatment for undescended testis at an early age can prevent testicular cancer.

See P. 1835

Long-Term Effect of Diabetes and Its Treatment on Cognitive Function

Improved glycemic control reduces complications in type 1 diabetes, but tight control of glucose is associated with more hypoglycemic episodes. The long-term effect of recurrent hypoglycemic events on cognitive function is not known. In this 18-year follow-up of patients enrolled in the Diabetes Control and Complications Trial, relatively high rates of severe hypoglycemic events were not associated with worse cognitive outcomes.

See P. 1842

Use of Physicians’ Services under Medicare’s Resource-Based Payments

In 1992, Medicare introduced the resource-based relative-value scale, which sets physicians’ payments on the basis of relative costs and assigns a number of relative-value units (RVUs) to each service. The use of physicians’ services (RVUs per Medicare beneficiary) grew by 45% between 1992 and 2002. Growth varied according to the type of service and specialty, with high rates of growth in cardiology and gastroenterology.

See P. 1853; Editorial, P. 1883

Superior Vena Cava Syndrome with Malignant Causes

A 58-year-old man presents with a 2-week history of progressive dyspnea on exertion, neck swelling, decreased appetite, and fatigue. There is no history of syncope or dysphagia. He smoked cigarettes until 5 years ago. The physical examination reveals a heart rate of 105 beats per minute, a respiratory rate of 20 breaths per minute, and superficial vascular distention over the neck, chest, and upper abdomen. Stridor is not present. How should his case be evaluated and managed?

See P. 1862; CME, P. 1901

The Drenched Doctor

A 55-year-old male physician was seen in August because of a 1-week history of fever and night sweats. The sweats required at least one nightly change of his pajamas and pillowcase. The patient also noted a worsening cough, which had previously been ascribed to esophageal reflux. There was no sputum production, photophobia, rash, arthralgia, dysuria, or change in bowel function.

See P. 1871
Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

Dennis M. Black, Ph.D., Pierre D. Delmas, M.D., Ph.D., Richard Eastell, M.D., Ian R. Reid, M.D., Steven Boonen, M.D., Ph.D., Ping Chung Leung, M.D., Zulema Man, M.D., Carlos Mautalen, M.D., Peter Mesenbrink, Ph.D., Huilin Hu, Ph.D., John Caminis, M.D., Karen Tong, B.S., Theresa Rosario-Jansen, Ph.D., Joel Krasnow, M.D., Trisha F. Hue, M.P.H., Deborah Sellmeyer, M.D., Erik Fink Eriksen, M.D., D.M.Sc., and Steven R. Cummings, M.D., for the HORIZON Pivotal Fracture Trial*

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*Investigators for the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial are listed in the Appendix.


BACKGROUND
A single infusion of intravenous zoledronic acid decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis. We assessed the effects of annual infusions of zoledronic acid on fracture risk during a 3-year period.

METHODS
In this double-blind, placebo-controlled trial, 3889 patients (mean age, 73 years) were randomly assigned to receive a single 15-minute infusion of zoledronic acid (5 mg) and 3876 were assigned to receive placebo at baseline, at 12 months, and at 24 months; the patients were followed until 36 months. Primary end points were new vertebral fracture (in patients not taking concomitant osteoporosis medications) and hip fracture (in all patients). Secondary end points included bone mineral density, bone turnover markers, and safety outcomes.

RESULTS
Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% during a 3-year period, as compared with placebo (3.3% in the zoledronic-acid group vs. 10.9% in the placebo group; relative risk, 0.30; 95% confidence interval [CI], 0.24 to 0.38) and reduced the risk of hip fracture by 41% (1.4% in the zoledronic-acid group vs. 2.5% in the placebo group; hazard ratio, 0.59; 95% CI, 0.42 to 0.83). Non-vertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively (P<0.001 for all comparisons). Zoledronic acid was also associated with a significant improvement in bone mineral density and bone metabolism markers. Adverse events, including change in renal function, were similar in the two study groups. However, serious atrial fibrillation occurred more frequently in the zoledronic acid group (in 50 vs. 20 patients, P<0.001).

CONCLUSIONS
A once-yearly infusion of zoledronic acid during a 3-year period significantly reduced the risk of vertebral, hip, and other fractures. (ClinicalTrials.gov number, NCT00049829.)
Fractures are an important cause of disability among postmenopausal women, and the costs of medical care associated with osteoporosis are estimated to be more than $18 billion annually in the United States alone.\(^1\) Bisphosphonates, the most commonly used treatment for established osteoporosis, inhibit osteoclast-mediated bone resorption and reduce the risk of vertebral fracture. Two bisphosphonates, alendronate and risendronate, also have been shown to reduce nonvertebral and hip fractures in women with osteoporosis.\(^2-6\) However, adherence to oral treatment is problematic, and about half of patients for whom oral treatment is prescribed do not adhere to it after 1 year.\(^7,8\) Poor adherence has been shown to compromise the effectiveness of treatment against fracture and to increase the costs of medical care.\(^9,10\)

A single infusion of intravenous zoledronic acid has been reported to decrease bone turnover and improve bone density for at least 12 months after infusion,\(^11\) suggesting an enduring effect. In our study, annual infusions of zoledronic acid (5 mg) for 3 years were evaluated to determine whether they reduced the risk of vertebral, hip, and other types of fracture.

**Methods**

**Study Design**

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial was an international, multicenter, randomized, double-blind, placebo-controlled trial involving postmenopausal women with osteoporosis. Patients were randomly assigned to receive either a 15-minute intravenous administration of zoledronic acid (5 mg) or placebo at baseline (day 0), at 12 months, and at 24 months. In addition, all patients received oral daily calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU). Patients were monitored for 3 years with quarterly telephone interviews and clinic visits at months 6, 12, 24, and 36.

The study was jointly designed by members of the steering committee and the sponsor. The sponsor had responsibility for data collection and quality control. An independent data and safety monitoring board met semiannually to oversee the conduct of the study and monitor the safety of patients. A copy of the study database was periodically transferred to the University of California, San Francisco (UCSF), for reports to the data and safety monitoring board. Analyses for publication were the joint responsibilities of representatives of the sponsor and investigators at UCSF. The original analyses were performed by the sponsor but were independently confirmed by investigators at UCSF. All the authors contributed to the writing of the article, and approval from a majority of the 13-member steering committee, which included 2 representatives of the sponsor, was required.

**Patients**

Postmenopausal women between the ages of 65 and 89 years were eligible for inclusion if they had a bone mineral density T score of −2.5 or less at the femoral neck, with or without evidence of existing vertebral fracture, or a T score of −1.5 or less, with radiologic evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Previous use of oral bisphosphonates was allowed, with the duration of the washout period dependent on previous use (e.g., previous use of ≥48 weeks required 2 years of washout). Concomitant use of the following osteoporosis medications was allowed at baseline and during follow-up: hormone therapy, raloxifene, calcitonin, tibolone, tamoxifen, dehydroepiandrosterone, ipriflavone, and medroxyprogesterone. Patients were placed into one of two strata on the basis of whether they were taking osteoporosis medications at baseline. Patients in stratum 1 were not taking any osteoporosis medications at the time of randomization, whereas patients in stratum 2 were all taking an allowed medication. Patients who had previously taken bisphosphonates and met washout criteria could be randomly assigned to either stratum. Ineligibility criteria included any previous use of parathyroid hormone or sodium fluoride, use of anabolic steroids or growth hormone within 6 months before trial entry or oral or intravenous systemic corticosteroids within 12 months, and any previous use of strontium. Patients with a serum calcium level of more than 2.75 mmol per liter or less than 2.00 mmol per liter were ineligible, as were patients with a calculated creatinine clearance of less than 30.0 ml per minute at either of two baseline visits or urine dipstick results of more than 2+ for protein, without evidence of contamination or bacteriuria.

From February 2002 to June 2003, patients underwent randomization with the use of random permuted blocks within strata; the last closeout
visit occurred on June 15, 2006. All patients provided written informed consent, and the local institutional review board at each center approved the protocol.

**End Points**
The primary end points were new vertebral fractures (in stratum 1) and hip fracture (in both strata). Secondary efficacy end points included any nonvertebral fracture, any clinical fracture, and clinical vertebral fracture. Other secondary end points were changes in bone mineral density at the total hip, femoral neck, and lumbar spine and changes in markers of bone resorption (serum C-telopeptide of type I collagen) and formation (bone-specific alkaline phosphatase and N-terminal propeptide of type I collagen). Data for premenopausal normative markers were based on 2.5th and 97.5th percentiles derived from the Os des Femmes de Lyon (OFELY) study12,13 (Dellmas PD and Garnero P: personal communication).

Height was measured with the use of a stadiometer, where available, at baseline and at months 12, 24, and 36.14 All investigators who performed endpoint evaluations were unaware of patients’ study-group assignments.

**Efficacy Measurements**
Spinal lateral radiographs were obtained at baseline and at 12, 24, and 36 months or early termination for patients in stratum 1 and at baseline and at 36 months or early termination for patients in stratum 2. Vertebrae from T4 to L4 were evaluated by an expert reader at a central imaging laboratory (Synarc) with the use of quantitative morphometry and standard methods.14 Incident morphometric vertebral fractures were defined as a reduction in vertebral height of at least 20% and 4 mm by quantitative morphometry, confirmed by an increase of one severity grade or more on semiquantitative analysis.14 Prevalent fracture at baseline was defined by a height ratio of at least 3 SD below the vertebra-specific mean height ratio on quantitative reading with semiquantitative confirmation.15,16

Clinical fracture reports were obtained from patients at each contact. Nonvertebral fracture reports required central confirmation, which was performed at the UCSF Coordinating Center. Evidence included either a radiologic or surgical procedure report or a copy of the radiograph. Excluded were fractures of the toe, facial bone, and finger and those caused by excessive trauma (assessed centrally as sufficient to cause fracture in a person without osteoporosis). For clinical vertebral fractures, the community-obtained radiograph was compared with the baseline study radiograph by a central reader at Synarc, and semiquantitative confirmation was required.

Dual-energy x-ray absorptiometry of the hip was performed at baseline and at months 6, 12, 24,
and 36. Investigators and coordinators were unaware of study-group assignments of patients regarding the results of follow-up scans. Bone loss was monitored centrally and if a patient’s loss of bone mineral density at the total hip exceeded 8% at 1 year or 10% at 2 years, the site was notified, and the patient counseled regarding alternative treatment options. Measurements of bone mineral density at the lumbar spine were obtained for a subgroup of patients. All measurements of bone mineral density were corrected for site variations.

Levels of serum C-telopeptide of type I collagen and bone-specific alkaline phosphatase were measured in serum samples obtained after an overnight fast in a subgroup of about 600 patients from selected clinical sites. An additional cohort underwent measurement of levels of N-terminal propeptide of type I collagen from samples shipped to the central laboratory at ambient temperature. Samples obtained at all time points for each patient were analyzed in a single batch, whenever possible, at Synarc.

**ADVERSE EVENTS**

Safety was assessed by the recording of all adverse events and serious adverse events and by physical

| Table 1. Baseline Characteristics of the Patients.† |
|-----------------|-----------------|-----------------|
| **Variable**    | **Placebo**     | **Zoledronic Acid** |
| **Stratum — no. (%)†** | **(N = 3861)** | **(N = 3875)** |
| 1               | 3039 (78.7)     | 3045 (78.6)     |
| 2               | 822 (21.3)      | 830 (21.4)      |
| **Mean — yr**   | 73.0±5.40       | 73.1±5.34       |
| **Age group — no. (%)** |           |               |
| <70 yr          | 1174 (30.4)     | 1140 (29.4)     |
| 70–74 yr        | 1235 (32.0)     | 1238 (31.9)     |
| ≥75 yr          | 1452 (37.6)     | 1497 (38.6)     |
| **Body-mass index** | 25.4±4.3       | 25.1±4.3       |
| **Region — no. (%)** |           |               |
| Western Europe  | 1162 (30.1)     | 1160 (29.9)     |
| Eastern Europe  | 772 (20.0)      | 774 (20.0)      |
| North America or Oceania | 765 (19.8) | 766 (19.8) |
| Latin America   | 622 (16.1)      | 625 (16.1)      |
| Asia            | 540 (14.0)      | 550 (14.2)      |
| **T score at femoral neck — no. (%)** |           |               |
| Less than −2.5  | 2734 (70.8)     | 2814 (72.6)     |
| −2.5 to −1.5    | 1073 (27.8)     | 1002 (25.9)     |
| Greater than −1.5 | 38 (1.0)       | 35 (0.9)       |
| Missing data    | 16 (0.4)        | 24 (0.6)        |
| **Bone mineral density — g/cm²** |           |               |
| Femoral neck    | 0.53±0.064      | 0.53±0.062      |
| Total hip       | 0.65±0.091      | 0.65±0.090      |
| Lumbar spine‡   | 0.79±0.140      | 0.79±0.124      |
| **Prevalent vertebral fracture — no. (%)** |           |               |
| 0               | 1383 (35.8)     | 1457 (37.6)     |
| 1               | 1076 (27.9)     | 1093 (28.2)     |
| ≥2              | 1401 (36.3)     | 1323 (34.1)     |
| Missing data    | 1 (<0.1)        | 2 (<0.1)        |
examination, regular measurement of vital signs, and regular monitoring of hematologic, biochemical, and urinary values. Adverse events were categorized according to codes used in the Medical Dictionary for Regulatory Activities (MedDRA). The five most commonly reported symptoms that occurred within 3 days after an infusion of a study drug (post-dose symptoms) — pyrexia, influenza-like symptoms, myalgia, headache, and arthralgia — were analyzed individually and grouped.

To assess renal safety, serum creatinine was measured in a subgroup of 5035 patients 9 to 11 days after each infusion. A significant increase was defined as a rise of more than 0.5 mg per deciliter (44 μmol per liter) in the serum creatinine level, as compared with the baseline level before the first infusion. A total of 559 patients underwent 12-lead electrocardiography before and 9 to 11 days after the third infusion. Patients who were taking medications associated with QT-interval prolongation were excluded from this substudy. Adjudication or expert review was performed for several categories of adverse events, including ocular events, osteonecrosis of the jaw, hypocalcemia, renal events, incomplete fracture healing, cardiovascular events, hip and knee osteonecrosis, and death. Each adjudication committee created a set of predefined search terms on the basis of codes from MedDRA and the World Health Organization Drug Reference List. The adverse-event database was then searched for these terms. Investigators at each clinical center collected medical documentation for the cases. This documentation was forwarded to the expert panels, which performed event adjudication while members were unaware of study-group assignments. Maxillofacial events that were possibly associated with a diagnosis of osteonecrosis of the jaw were adjudicated on the basis of a definition of the disorder as the presence of exposed bone for more than 6 weeks.

**STATISTICAL ANALYSIS**

The plan for the analysis of data, which was developed before unblinding, prespecified all statistical analyses. Efficacy analyses included all patients who had undergone randomization, except for 29 patients from a site whose participation had been terminated during the study. Patients who had received at least one infusion were included in safety analyses (Fig. 1).

### Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 3861)</th>
<th>Zoledronic Acid (N = 3875)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous medication use — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>813 (21.1)</td>
<td>825 (21.3)</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>557 (14.4)</td>
<td>565 (14.6)</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>425 (11.0)</td>
<td>444 (11.5)</td>
</tr>
<tr>
<td>SERMs</td>
<td>412 (10.7)</td>
<td>434 (11.2)</td>
</tr>
<tr>
<td>Other</td>
<td>43 (1.1)</td>
<td>43 (1.1)</td>
</tr>
</tbody>
</table>

| Concomitant medications used by >5% of patients in stratum 2 — no. (%) | | |
| No. of patients | 822 | 830 |
| Raloxifene hydrochloride | 346 (42.1) | 345 (41.6) |
| Calcitonin (salmon) | 144 (17.5) | 137 (16.5) |
| Conjugated estrogens | 101 (12.3) | 109 (13.1) |
| Estradiol | 69 (8.4) | 68 (8.2) |

*Plus–minus values are means ±SD. The only category in which there was a significant difference between the study groups was body-mass index (P = 0.01). Body-mass index is the weight in kilograms divided by the square of the height in meters. A total of 14 patients in the zoledronic-acid group and 15 in the placebo group were excluded from all analyses because the participation of their clinical center was terminated, owing to issues associated with data reliability. Percentages may not total 100 because of rounding. SERM denotes selective estrogen-receptor modulator. †Patients in stratum 1 were not taking any concomitant osteoporosis medications at the time of randomization, whereas patients in stratum 2 were all taking an allowed medication. ‡The analysis of bone mineral density at the lumbar spine included 270 patients in the placebo group and 272 in the zoledronic-acid group.
The incidence of vertebral fracture (stratum 1) included patients who had undergone radiography at baseline and at least once during follow-up. An incident fracture was identified if at least one follow-up radiograph met the criteria for incident fracture. Results are presented as the relative risk and 95% confidence interval (CI).

Clinical fractures (including hip fracture) were analyzed with the use of a proportional-hazards model stratified for the study stratum, with the relative hazard reported and the cumulative proportion of patients with fractures estimated by means of Kaplan–Meier analysis. Follow-up time was defined as the time from randomization to the first relevant fracture, the last study visit, or the time of death, whichever occurred first. Changes in bone mineral density were compared with the use of analysis of variance adjusted for stratum and region. Changes in biochemical markers were compared by means of analysis of covariance (ANCOVA) (log, ratio of the post-baseline value to the baseline value) adjusted for stratum, center, and baseline value. The incidence of safety events was compared with the use of Fisher’s exact test.

One interim analysis of the two primary end points was conducted for the data and safety monitoring board and the final significance levels were adjusted accordingly to \( P = 0.0496 \) for vertebral fracture and \( P = 0.0406 \) for hip fracture. For all other tests, a \( P \) value of 0.05 or less was considered to indicate statistical significance. All reported \( P \) values are two-sided. No adjustments were made for multiple comparisons of the safety end points.

The study had a power of 90% (with a two-sided alpha of 0.05) to detect a 50% reduction in morphometric vertebral fractures in the zoledronic-acid group, assuming an annual incidence of 1.9% in the placebo group, with 2252 patients in stratum 1 (the number that was originally projected). With 7400 patients, the log-rank test had a power of 0.05 to detect a 50% reduction in hip fractures, assuming a 3-year fracture rate of 1.8% in the placebo group.

The mean age of patients was 73 years, with approximately half from Europe and half from North and South America and Asia (Table 1). For measures of bone mineral density at the femoral neck, 72% of the patients had T scores below –2.5, 63% had baseline vertebral fractures, and 79% were in stratum 1. Among 1652 patients in stratum 2, the number of patients who were taking raloxifene (42%) was larger than that of patients taking any other medication. A total of 6517 patients (84%) remained in active follow-up through 3 years. A total of 6260 patients (81%) received all three infusions.

BONE MINERAL DENSITY AND BIOCHEMICAL MARKERS
In the zoledronic-acid group, bone mineral density increased significantly at the total hip (6.02%; 95% CI, 5.77 to 6.28), lumbar spine (6.71%; 95% CI, 5.69 to 7.74), and femoral neck (5.06%; 95% CI, 4.76 to 5.36), as compared with the placebo group (\( P < 0.001 \) for all comparisons) (Fig. 3). All three biochemical markers of bone turnover decreased significantly in patients in the zoledronic-acid group, as compared with those in the placebo group (Fig. 3). At 12 months, levels of serum C-telopeptide of type I collagen, bone-specific alkaline phosphatase, and N-terminal propeptide of type I collagen were 59% (95% CI, 55 to 63), 30% (95% CI, 27 to 32), and 58% (95% CI, 55 to 60) lower, respectively, in the zoledronic-acid group (\( P < 0.001 \) for all com-
Adverse Events

The numbers of patients who died, had a serious adverse event, or discontinued follow-up because of an adverse event did not significantly differ between the study groups (Table 3), although the number of patients with adverse events was significantly higher in the zoledronic-acid group (95.5% vs. 93.9%), primarily because of a larger number of post-dose symptoms. At 9 to 11 days after infusion, 1.3% of patients in the zoledronic-acid group had an increase of more than 0.5 mg per deciliter in the serum creatinine level, as compared with 0.4% in the placebo group. However, these changes were transient; within 30 days, the levels in more than 85% of patients had returned to within 0.5 mg per deciliter of preinfusion values, and the remainder had returned to this level by the next annual follow-up. At 3 years, there was no significant difference in either serum creatinine levels or creatinine clearance between the groups. The number of patients who had any of the five most frequently reported symptoms after the first infusion was significantly higher in the zoledronic-acid group than in the placebo group, but the number with symptoms after subsequent infusions decreased substantially. Other, less common, symptoms, including chills, nausea, bone pain, and back pain, were reported more frequently in the zoledronic-acid group. These symptoms were generally rated as mild to moderate and resolved within 3 days.

The number of patients who had arrhythmia in the zoledronic-acid group (266 patients, or 6.9%) was significantly higher than that in the placebo group (203 patients, or 5.3%; P = 0.003). Serious atrial fibrillation, a subcategory of all arrhythmias, was more common among patients in the zoledronic-acid group. A total of 50 patients in the zoledronic-acid group had serious atrial fibrillation (1.3%), as compared with 20 patients (0.5%) in the placebo group (P<0.001). After adjudication, the number of patients whose atrial fibrillation was reported as a serious adverse event did not change appreciably (50 in the zoledronic-acid group and 17 in the placebo group). Among the 50 patients, the events occurred more than 30 days after infusion in 47 patients. Among 559 patients who underwent electrocardiography, the prevalence of atrial fibrillation (2.1% in the zoledronic-acid group and 2.8% in the placebo group) and other electrocardiographic abnormalities did not differ significantly between the study groups. No difference was observed in the occurrence of the serious adverse events of stroke (2.3% in both study groups); the incidence of death due to stroke was 0.5% in the zoledronic-acid group and 0.3% in the placebo group (P=0.15) (Table 3).

### Table 2. Relative Risk of Fracture Incidence in the Two Study Groups.†

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Placebo</th>
<th>Zoledronic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphometric vertebral fracture (stratum 1)</td>
<td>310 (10.9)</td>
<td>92 (3.3)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>88 (2.5)</td>
<td>52 (1.4)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvertebral fracture</td>
<td>388 (10.7)</td>
<td>292 (8.0)</td>
</tr>
<tr>
<td>Any clinical fracture</td>
<td>456 (12.8)</td>
<td>308 (8.4)</td>
</tr>
<tr>
<td>Clinical vertebral fracture</td>
<td>84 (2.6)</td>
<td>19 (0.5)</td>
</tr>
<tr>
<td>Multiple (=2) morphometric vertebral fractures (stratum 1)</td>
<td>66 (2.3)</td>
<td>7 (0.2)</td>
</tr>
</tbody>
</table>

* The percentage of morphometric fractures is the proportion of patients with a baseline radiograph, at least one follow-up radiograph, and a fracture (2853 patients in the placebo group and 2822 patients in the zoledronic-acid group). The percentage of clinical fractures is based on Kaplan–Meier estimates of the 3-year cumulative incidence (3875 patients with clinical fractures in the placebo group and 3861 in the zoledronic-acid group).
† For morphometric vertebral fractures, the relative risk is presented; for all other end points, the adjusted hazard ratio is presented. The significance level for morphometric vertebral fractures is based on an adjusted logistic-regression analysis.
There were no spontaneous reports of osteonecrosis of the jaw. From a search of the trial database of adverse events, which was followed by expert adjudication, two cases of potential osteonecrosis of the jaw were identified (one in the placebo group and one in the zoledronic-acid group). In both patients, delayed healing followed surgical manipulation, and both cases subsequently resolved with antibiotic therapy and débridement. A similar search for and review of osteonecrosis of the hip or knee revealed seven cases (three in the placebo group and four in the zoledronic-acid group). No adverse effect on fracture healing was observed, with three cases of nonunion (one in the placebo group and two in the zoledronic-acid group).

At 9 to 11 days after the first infusion, 49 patients in the zoledronic-acid group had a serum calcium level of less than 2.075 mmol per liter, as compared with 1 patient in the placebo group. All events were transient and asymptomatic. Patients who were treated with zoledronic acid had an absolute increase of approximately 0.69% (3.34% vs. 2.65%) in inflammatory ocular adverse events (mainly conjunctivitis) during the first 15 days after infusion.

**DISCUSSION**

During a 3-year period, an annual infusion of 5 mg of zoledronic acid significantly reduced the risk of fracture at all key osteoporotic fracture sites, including the two primary end points, vertebral and hip fractures. The 70% reduction in the vertebral-fracture rate was greater than the 3-year reduction previously observed for oral bisphosphonates (40 to 50%).\(^2\,4,6,18-20\) and the reductions in fracture rates associated with other antiresorptive agents.\(^21\,23\) All other prospectively defined categories of fracture, including nonvertebral fractures and clinical vertebral fractures, were also significantly reduced (P<0.001 for all comparisons).

A regimen of infusions once a year appears to ensure that patients will have a full treatment effect for at least 12 months. In contrast, many patients who receive prescriptions for oral bisphosphonates stop treatment, and most appear to be taking less than 80% of their prescribed pills by 12 months.\(^19\,24\,25\) Adherence to a regimen of oral bisphosphonates is challenging because the drug must be taken with a full glass of water when the patient is fasting, and the patient must remain upright for at least 30 minutes after taking the medication. Since poor adherence reduces the anti-fracture efficacy,\(^9\) a single annual infusion of zoledronic acid might improve such efficacy in clinical practice.

The effect of zoledronic acid on biochemical markers in our study was similar to that reported for oral bisphosphonates.\(^4,19,20,27-30\) Furthermore, levels of bone remodeling associated with zoledronic acid during a 3-year period improves bone strength without adversely affecting remodeling capacity.

As reported with other bisphosphonates that are administered intravenously, mild-to-moderate post-dose symptoms occurred most commonly after the first infusion. These symptoms typically resolved within 3 days after their onset and declined markedly with subsequent infusions. Treatment with antipyretic analgesics (e.g., ibuprofen and acetaminophen) appeared to mitigate these symptoms.

The study protocol included monitoring for adverse renal effects 9 to 11 days after each infusion. As reported with other bisphosphonates that are administered intravenously, mild-to-moderate post-dose symptoms occurred most commonly after the first infusion. These symptoms typically resolved within 3 days after their onset and declined markedly with subsequent infusions. Treatment with antipyretic analgesics (e.g., ibuprofen and acetaminophen) appeared to mitigate these symptoms.

The number of subjects at 36 months is the number who had closeout visits on or after the start of the 36-month window for visits.
Inflammatory ocular adverse events within the first 15 days after infusion, as reported with other bisphosphonates. All such events were treated and resolved with outpatient treatment. Most cases of osteonecrosis of the jaw have been observed in patients with cancer who were treated with frequent doses of intravenous bisphosphonates. Our study assessed the incidence of osteonecrosis of the jaw, a rare but severe complication of bisphosphonate therapy. The incidence of osteonecrosis of the jaw was low and similar in the zoledronic acid and placebo groups. The risk of adverse events, including osteonecrosis of the jaw, was low and similar between the two groups. The cumulative incidence of adverse events was also low and similar between the two groups. The hazard ratio for zoledronic acid versus placebo was 0.75 (95% CI, 0.64–0.87) P<0.001. The hazard ratio for the combined endpoint of any clinical fracture and nonvertebral fracture was 0.59 (95% CI, 0.42–0.83) P=0.002. The hazard ratio for clinical vertebral fracture was 0.67 (95% CI, 0.58–0.77) P<0.001. The hazard ratio for hip fracture was 0.23 (95% CI, 0.14–0.37) P<0.001. The hazard ratio for nonvertebral fracture was 0.75 (95% CI, 0.64–0.87) P<0.001. The hazard ratio for the combined endpoint of any clinical fracture and nonvertebral fracture was 0.59 (95% CI, 0.42–0.83) P=0.002. The hazard ratio for clinical vertebral fracture was 0.67 (95% CI, 0.58–0.77) P<0.001. The hazard ratio for hip fracture was 0.23 (95% CI, 0.14–0.37) P<0.001. The hazard ratio for nonvertebral fracture was 0.75 (95% CI, 0.64–0.87) P<0.001.
osteonecrosis of the jaw prospectively in a large number of women with osteoporosis who were receiving a bisphosphonate. There were no spontaneous reports of osteonecrosis of the jaw by patients in our study. In addition, blinded adjudication of the safety database yielded one case in the zoledronic-acid group and one in the placebo group, suggesting that the risk of osteonecrosis of the jaw in women with postmenopausal osteoporosis is very low and that this disorder may occur...
without bisphosphonate treatment. A once-yearly regimen with intravenous zoledronic acid does not appear to affect the frequency of this adverse event.

An increased incidence of serious atrial fibrillation was observed in the zoledronic-acid group, as compared with the placebo group. The events were uniformly distributed over time, with the vast majority of events occurring more than 30 days after infusion, by which time zoledronic acid is undetectable in the circulation. There are no studies establishing biologic mechanisms that might link bisphosphonate therapy to atrial fibrillation or arrhythmia. Alterations in serum calcium levels could be related to atrial fibrillation, but the administration of zoledronic acid had little or no

### Table 3. Adverse Events.\(^\ast\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 3852) no. of patients (%)</th>
<th>Zoledronic Acid (N = 3862) no. of patients (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>3616 (93.9)</td>
<td>3688 (95.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>1158 (30.1)</td>
<td>1126 (29.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Death</td>
<td>112 (2.9)</td>
<td>130 (3.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Discontinuation of follow-up owing to adverse event</td>
<td>70 (1.8)</td>
<td>80 (2.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>Renal events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in serum creatinine &gt;0.5 mg/dl(\dagger)</td>
<td>10 (0.4)</td>
<td>31 (1.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary protein &gt;2+(\dagger)</td>
<td>5 (0.2)</td>
<td>13 (0.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Calculated creatinine clearance &lt;30 ml/min</td>
<td>152 (3.9)</td>
<td>160 (4.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Five most common post-dose symptoms (≤3 days after infusion)(\ddagger)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>79 (2.1)</td>
<td>621 (16.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>66 (1.7)</td>
<td>365 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>61 (1.6)</td>
<td>301 (7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>90 (2.3)</td>
<td>273 (7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>76 (2.0)</td>
<td>245 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any of the five most common post-dose symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After first infusion</td>
<td>237 (6.2)</td>
<td>1221 (31.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After second infusion</td>
<td>79 (2.1)</td>
<td>253 (6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After third infusion</td>
<td>42 (1.1)</td>
<td>108 (2.8)</td>
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</tr>
<tr>
<td>Cardiovascular events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>73 (1.9)</td>
<td>94 (2.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>20 (0.5)</td>
<td>50 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke(\ddagger)</td>
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<td></td>
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<tr>
<td>Serious adverse event</td>
<td>88 (2.3)</td>
<td>87 (2.3)</td>
<td>0.94</td>
</tr>
<tr>
<td>Death from stroke</td>
<td>11 (0.3)</td>
<td>20 (0.5)</td>
<td>0.15</td>
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<tr>
<td>Myocardial infarction</td>
<td>45 (1.2)</td>
<td>38 (1.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>33 (0.9)</td>
<td>39 (1.0)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

* Adverse events were categorized according to codes used in the Medical Dictionary for Regulatory Activities (MedDRA).
† The increase was based on dipstick measurements before infusion of a study drug as compared with those 9 to 11 days after infusion, as evaluated in 2514 patients in the placebo group and 2521 in the zoledronic-acid group.
‡ Listed are the five most common adverse events reported within 3 days after infusion in the zoledronic-acid group.
§ The category of stroke included selected relevant terms for nervous system disorders from MedDRA that had been pre-defined for reporting strokes for regulatory submissions. Death from cardiovascular causes included any death in which the preferred term for the cause was listed for cardiac events in MedDRA.
effect on serum calcium levels measured 9 to 11 days after infusion. Electrocardiography that was performed before and 9 to 11 days after the third infusion in 559 patients who were not taking drugs that cause prolongation of QT intervals showed no significant difference between groups in the prevalence of arrhythmia. However, low-frequency, intermittent arrhythmia might not have been captured on the short echocardiogram in this subgroup. An increased risk of serious atrial fibrillation had not been previously associated with zoledronic acid or other bisphosphonates, although a letter in this issue of the Journal reports a similar, though nonsignificant, trend from the 1997 Fracture Intervention Trial of alendronate. The observed association might be due to chance but should be further explored in other trials of zoledronic acid and reanalyses of data from other bisphosphonate trials.

In conclusion, a once-yearly infusion of zoledronic acid during a 3-year period was associated with a significant and sustained decrease in the risk of vertebral, hip, and other fractures. In addition, the treatment had a favorable safety profile and was generally well tolerated. Given the relatively poor adherence to oral bisphosphonate therapy in clinical practice, annual infusion of zoledronic acid may provide a promising approach to reducing fracture risk.

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References


24. Cooper AL. Improved patient persistence on once-monthly dosing regime plus patient support compared with a weekly regime. Presented at the International Osteoporosis Foundation World Congress on Osteoporosis, Toronto, June 2-6, 2006 (poster).


31. Fraunfelder FW, Fraunfelder FT. 3
Once-Yearly Zoledronic Acid for Postmenopausal Osteoporosis


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Intracoronary Streptokinase after Primary Percutaneous Coronary Intervention

Murat Sezer, M.D., Hüseyin Oflaz, M.D., Taner Gören, M.D., İrem Okçular, M.D., Berrin Umman, M.D., Yılmaz Nişancı, M.D., Ahmet Kaya Bilge, M.D., Yasemin Şanli, M.D., Mehmet Meriç, M.D., and Sabahattin Umman, M.D.

ABSTRACT

BACKGROUND
Microvascular perfusion is often impaired after primary percutaneous coronary intervention (PCI). We proposed that in situ thrombosis might contribute to poor myocardial perfusion in this setting. To test this hypothesis, we evaluated the effect of low-dose intracoronary streptokinase administered immediately after primary PCI.

METHODS
Forty-one patients undergoing primary PCI were randomly assigned to receive intracoronary streptokinase (250 kU) or no additional therapy. Two days later, cardiac catheterization was repeated, and coronary hemodynamic end points were measured with the use of a guidewire tipped with pressure and temperature sensors. In patients with anterior myocardial infarction, the deceleration time of coronary diastolic flow was measured with transthoracic echocardiography. At 6 months, angiography, echocardiography, and technetium-99m single-photon-emission computed tomography were performed.

RESULTS
Two days after PCI, all measures of microvascular function (means ±SD) were significantly better in the streptokinase group than in the control group, including coronary flow reserve (2.01±0.57 vs. 1.39±0.31), the index of microvascular resistance (16.29±5.06 U vs. 32.49±11.04 U), the collateral-flow index (0.08±0.05 vs. 0.17±0.07), mean coronary wedge pressure (10.81±5.46 mm Hg vs. 17.20±7.93 mm Hg), systolic coronary wedge pressure (18.24±6.07 mm Hg vs. 33.80±11.00 mm Hg), and diastolic deceleration time (828±258 msec vs. 360±292 msec). The administration of intracoronary streptokinase was also associated with a significantly lower corrected Thrombolysis in Myocardial Infarction frame count (the number of cine frames required for dye to travel from the ostium of a coronary artery to a standardized distal coronary landmark) at 2 days. At 6 months, however, there was no evidence of a difference between the two study groups in left ventricular size or function.

CONCLUSIONS
In our pilot trial, the administration of low-dose intracoronary streptokinase immediately after primary PCI improved myocardial reperfusion but not long-term left ventricular size or function. These findings require clarification in a larger trial. (ClinicalTrials.gov number, NCT00302419.)
Primary percutaneous coronary intervention (PCI) is an established reperfusion strategy in the treatment of acute myocardial infarction with ST-segment elevation.1 Nevertheless, myocardial damage is not immediately terminated after the elimination of epicardial occlusion with successful primary PCI. It has been presumed that reperfusion injury and embolization of epicardial thrombus and plaque debris jeopardize tissue-level perfusion.2-4 Although thromboembolism of proximal origin may limit microvascular perfusion,5,6 a thrombus may also form in the microvasculature itself. This concept may help explain why recent randomized trials have failed to show a beneficial effect of distal protection devices on microvascular perfusion during primary PCI, despite effective retrieval of thrombus and plaque content from epicardial coronary arteries.7,8

We proposed that the intracoronary infusion of low-dose streptokinase immediately after primary PCI might further improve tissue-level perfusion by dissolving thrombi (either formed in situ or embolic) at the microvascular level. This hypothesis was investigated prospectively in a pilot trial.

Methods

Patients

Patients who had their first ST-segment elevation and were scheduled to undergo primary PCI within 12 hours after the onset of symptoms were considered for trial enrollment. Inclusion criteria were ongoing chest pain, ST-segment elevation on electrocardiography, and occlusion of the infarct-related artery (Thrombolysis in Myocardial Infarction [TIMI] flow grade of 0 or 1) on angiography. The main exclusion criteria were the presence of the culprit lesion in a saphenous-vein graft, an additional lesion causing more than 50% narrowing distal to the culprit lesion, or a left bundle-branch block; history of prior myocardial infarction; and contraindications to streptokinase, tirofiban, aspirin, clopidogrel, or heparin. Written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by our hospital ethics committee.

Study Protocol

Immediately after diagnostic angiography, eligible patients were assigned to either the streptokinase group or the control group (which received no additional therapy) according to a computer-generated random sequence. In both groups, primary PCI was performed with the use of stent implantation after balloon dilation. All patients received 300 mg of aspirin; a loading dose of 600 mg of clopidogrel; an intracoronary infusion of unfractionated heparin at a dose of 100 U per kilogram of body weight during the procedure; tirofiban as a bolus of 0.1 μg per kilogram 3 minutes after the start of the procedure, followed by continuous infusion of tirofiban at 0.15 μg per kilogram per minute for 12 hours; and low-molecular-weight heparin initiated 4 to 5 hours after primary PCI and continued for at least 48 hours. After PCI, coronary angiography was repeated to assess the corrected TIMI frame count,9 the number of cine frames required for dye to travel from the ostium of a coronary artery to a standardized distal coronary landmark, and the myocardial blush grade.10

In the streptokinase group, immediately after the postprocedure coronary angiography, 250 kU of streptokinase diluted with 20 ml of saline was infused through the guiding catheter for 3 minutes. The control group received no additional treatment. Electrocardiograms were recorded both immediately and 60 minutes after the PCI to assess the resolution of ST-segment deviation.11

The femoral sheath was removed as soon as the activated partial-thromboplastin time was appropriate (first checked 4 hours after the conclusion of the PCI), and hemostasis was achieved by manual compression. During the period of hospitalization, patients were monitored carefully for bleeding at the femoral access site and other bleeding complications. Prespecified medications consisted of 100 mg of aspirin daily for an indefinite period, 75 mg of clopidogrel daily for 1 year, and the maximum tolerated doses of beta-blockers and angiotensin-converting–enzyme inhibitors if not contraindicated.

Intracoronary Hemodynamic Measurements and Angiographic Analysis

Two days after primary PCI, all patients underwent a second cardiac catheterization for evaluation of microvascular function. Several distinct assessments were performed during this evaluation, including angiography and measurement of intracoronary hemodynamic characteristics.

For the assessment of hemodynamic characteristics, a guidewire tipped with pressure and
temperature sensors (PressureWire Sensor, Radi Medical Systems) was positioned distal to the stented segment of the infarct-related artery. Papaverine was used as the hyperemic agent. The transit time (in seconds) of room-temperature saline injected into a coronary artery at rest and during hyperemia was measured three times and averaged, as previously described.12 The thermodilution-derived coronary flow reserve was calculated as the mean transit time at rest divided by the mean transit time during hyperemia.13 The index of microvascular resistance (in mm Hg–seconds, or units) was defined as the distal coronary pressure multiplied by the mean transit time during hyperemia. For this calculation, central venous pressure was not measured directly but was estimated as 5 mm Hg, as described elsewhere.15 All coronary hemodynamic data were recorded, stored off-line, and analyzed by an independent investigator who was unaware of the group assignments.

Coronary angiography was also performed 2 days after primary PCI. The corrected TIMI frame count and myocardial blush grade were determined from the appropriate angiographic images.

NONINVASIVE ASSESSMENT OF MICROVASCULAR PERFUSION

Two days after primary PCI, the coronary flow-velocity pattern was assessed with the use of transthoracic echocardiography (as previously described16) in patients in whom the infarct-related artery was the left anterior descending coronary artery. The deceleration time of coronary diastolic flow was measured with the use of the coronary flow-velocity spectrum.17

LONG-TERM FOLLOW-UP

Echocardiography, angiography, and technetium-99m–labeled sestamibi single-photon-emission computed tomography (SPECT) were performed 6 months after primary PCI. Left ventricular end-diastolic and end-systolic volumes were measured, and the percent changes relative to the values 2 days after PCI were calculated. Patients with 70% or more stenosis in the stented segment on angiography were excluded from the volume analysis at 6 months to avoid the confounding effect of re-stenosis of the infarct-related artery. TIMI frame count and myocardial blush grade were reassessed on the follow-up angiogram. Technetium-99m–labeled sestamibi SPECT was used to measure infarct size, expressed as a percentage of the total area of the myocardium,18 by a nuclear medicine specialist who was unaware of the group assignments.

STUDY END POINTS

We designated several measures as primary end points, including coronary flow reserve, index of microvascular resistance, coronary wedge pressure, collateral-flow index, and coronary diastolic deceleration time. The secondary end points included the corrected TIMI frame count, myocardial blush grade, infarct size, changes in left ventricular volume, and major adverse cardiac events such as re-infarction, revascularization, and death.

STATISTICAL ANALYSIS

Estimated mean values for each of the primary end points were obtained from the published literature. Using GraphPad Instat software, we then calculated the number of patients that would be necessary to detect a difference of 30% between the streptokinase group and the control group for each end point, with an α of 0.05, a β of 0.20, and a statistical power of 0.80. The necessary number of patients ranged from 7 to 39 patients per group, depending on the end point. Therefore, we targeted a sample of 40 patients per group. However, at a preplanned interim analysis (including approximately half the target study sample), significant absolute differences of more than 30% between the two study groups were demonstrated for most of the primary end points (excluding the coronary diastolic deceleration time, which is reported not to have a normal distribution). The decision was therefore made to terminate enrollment.

All statistical tests were performed with SPSS software, version 7.5. Group percentages were compared with the use of the chi-square test or Fisher’s exact test, as appropriate. Group means for variables with normal and nonnormal distributions were compared with the use of Student’s t-test for independent groups and the Mann–Whit-
ney U test, respectively. All analyses were repeated for the subgroup of patients with anterior myocardial infarction (in whom the infarct-related artery was the left anterior descending coronary artery). Group means were also adjusted for possible confounding factors (age; time from chest pain that has persisted for 30 minutes to balloon dilation [pain-to-balloon time]; presence or absence of diabetes, hypertension, hyperlipidemia, angina before myocardial infarction, slow flow, and side-branch embolization; smoking status; and infarct location) with the use of analysis of covariance. The difference between groups with regard to myocardial blush grade 0 or 1 was first analyzed with the use of the chi-square test and then with a logistic-regression model including age and pain-to-balloon time, in addition to the study-group variable (intracoronary streptokinase or no treatment). Two-tailed P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

STUDY PATIENTS AND ANGIOGRAPHIC OUTCOMES

Between October 2004 and March 2006, 41 patients were enrolled and randomly assigned to receive either intracoronary streptokinase (21 patients) or no additional treatment (20 patients) (Fig. 1). Baseline demographic, clinical, and angiographic characteristics are listed in Table 1. There were no significant differences between the two groups. All patients but one were male, and the mean age was 51.8 years.

The infarct-related artery was successfully opened in all patients, each of whom received at least one stent. No major bleeding or groin complications occurred. Minimal bleeding (according to the TIMI bleeding classifications) was observed at the femoral access site in one patient in each group and was managed with manual compression. During postprocedural assessment, a femoral pseudoaneurysm was detected in one patient in the streptokinase group and was also managed with manual compression.

ASSESSMENT OF MICROCIRCULATION

Intracoronary hemodynamic end points were evaluated at a mean (±SD) of 48±10 hours after primary PCI. Microvascular perfusion was significantly better in the streptokinase group than in the control group with regard to all the primary end points (Table 2). Coronary flow reserve was significantly greater in the streptokinase group than in the control group (2.01±0.57 vs. 1.39±0.31, adjusted P=0.002). Other end points were significantly lower in the streptokinase group than in the control group: the index of microvascular resistance (16.29±5.06 U vs. 32.49±11.04 U, adjusted P<0.001), collateral-flow index (0.08±0.05 vs. 0.17±0.07, adjusted P=0.002), mean coronary wedge pressure (10.81±5.46 mm Hg vs. 17.20±7.93 mm Hg, adjusted P=0.04), and systolic coronary wedge pressure (18.24±6.07 mm Hg vs. 33.80±11.00 mm Hg, adjusted P<0.001).

The infarct-related artery was the left anterior descending coronary artery in 30 patients. In these patients, the diastolic deceleration time of the recanalized artery was significantly longer in the streptokinase group than in the control group (828±258 msec vs. 360±292 msec, adjusted P=0.001) (Table 2).

Immediately after primary PCI, there were no significant differences between the two groups with regard to corrected TIMI frame count or myocardial blush grade. However, at 2 days after PCI, the corrected TIMI frame count was significantly lower in the streptokinase group than in the control group (22.52±5.58 vs. 31.79±7.58, adjusted P=0.001). The myocardial blush grade at 2 days did not differ significantly between the two groups after multivariate adjustment (Table 2).

There was no significant difference between the streptokinase group and the control group with respect to the mean initial ST-segment elevation across all affected leads or the percent resolution of ST-segment deviation immediately after PCI. Sixty minutes after PCI, the percent resolution of ST-segment deviation was higher in the streptokinase group than in the control group, but this difference was not significant after multivariate adjustment (Table 2).

LONG-TERM RESULTS

Echocardiography, SPECT, and coronary angiography were performed 7.5±2.4 months after primary PCI for purposes of long-term reassessment (Fig. 1). Univariate analyses showed that infarct size was smaller, ventricular volumes were less, ejection fraction was higher, and myocardial perfusion was better in the streptokinase group than in the control group (Table 3). However, after multivariate analysis, only the differences between the
Figure 1. Enrollment, Randomization, and Follow-up of Study Patients.

Twenty patients in each group were available for clinical follow-up at a mean (±SD) of 7.5±2.4 months after primary percutaneous coronary intervention (PCI). SPECT denotes single-photon-emission computed tomography, and CABG coronary-artery bypass grafting.
### Table 1. Baseline Demographic, Clinical, and Angiographic Characteristics. a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Streptokinase Group (N = 21)</th>
<th>Control Group (N = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main characteristics</strong></td>
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<td></td>
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<tr>
<td>Age — yr</td>
<td>51.4±5.7</td>
<td>52.2±10.9</td>
<td>0.79</td>
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<td>Male sex — no. (%)</td>
<td>21 (100)</td>
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<td>Smoking — no. (%)</td>
<td>17 (81)</td>
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<td>0.65</td>
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<td>Diabetes mellitus — no. (%)</td>
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<td>3 (15)</td>
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<td>Hypertension — no. (%)</td>
<td>4 (19)</td>
<td>7 (35)</td>
<td>0.20</td>
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<td>Dyslipidemia — no. (%)</td>
<td>12 (57)</td>
<td>14 (70)</td>
<td>0.27</td>
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<td>History of angina before infarction — no. (%)</td>
<td>5 (24)</td>
<td>5 (25)</td>
<td>0.85</td>
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<td>Infarct location — no. (%)</td>
<td></td>
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</tr>
<tr>
<td>Anterior</td>
<td>14 (67)</td>
<td>16 (80)</td>
<td></td>
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<tr>
<td>Nonanterior</td>
<td>7 (33)</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>Peak troponin T concentration — ng/ml</td>
<td>9.1±6.5</td>
<td>10.4±7.6</td>
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<td>Initial ST elevation — mm</td>
<td>15.6±10.5</td>
<td>19.0±9.7</td>
<td>0.18</td>
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<td><strong>Concomitant medication use during PCI and in the coronary care unit</strong></td>
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<td></td>
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<tr>
<td>Aspirin — no. (%)</td>
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<td>20 (100)</td>
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<td>Beta-blocker — no. (%)</td>
<td>19 (90)</td>
<td>18 (90)</td>
<td>0.96</td>
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<td>Low-molecular-weight heparin — no. (%)</td>
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<td>20 (100)</td>
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<td>Glycoprotein IIb/IIIa inhibitor — no. (%)</td>
<td>21 (100)</td>
<td>20 (100)</td>
<td>1.00</td>
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<td>Clopidogrel — no. (%)</td>
<td>21 (100)</td>
<td>20 (100)</td>
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<td>Statins — no. (%)</td>
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<td>18 (90)</td>
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<td>Intravenous nitroglycerin — no. (%)</td>
<td>16 (76)</td>
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<td>ACE inhibitor — no. (%)</td>
<td>19 (90)</td>
<td>16 (80)</td>
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<td><strong>Angiographic characteristics</strong></td>
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<td>Infarct-related coronary artery — no. (%)</td>
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<td>LAD</td>
<td>14 (67)</td>
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<td>RCA</td>
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<tr>
<td>CX</td>
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<td>1 (5)</td>
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<td>No. of diseased vessels — no. (%)</td>
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<td></td>
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<tr>
<td>1</td>
<td>16 (76)</td>
<td>14 (70)</td>
<td>0.73</td>
</tr>
<tr>
<td>2</td>
<td>4 (19)</td>
<td>4 (20)</td>
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<tr>
<td>3</td>
<td>1 (5)</td>
<td>2 (10)</td>
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<tr>
<td>Baseline TIMI flow grade 0 or 1 — %</td>
<td>100</td>
<td>100</td>
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<td>Pain-to-balloon time — min</td>
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<td><strong>Postprocedural results</strong></td>
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<td>Slow or no reflow — no. (%)</td>
<td>5 (23)</td>
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<td>Side-branch embolization — no. (%)</td>
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<td>Maximal inflation pressure — atm</td>
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<td>No. of stents</td>
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<td>3.5±2.8</td>
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<td>TIMI flow grades — no. (%)</td>
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<td>0 or 1</td>
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<tr>
<td>3</td>
<td>16 (76)</td>
<td>18 (90)</td>
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</tr>
<tr>
<td>Procedural complications — no.</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

a Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, LAD left anterior descending coronary artery, RCA right coronary artery, CX left circumflex coronary artery, and TIMI Thrombolysis in Myocardial Infarction trial.
two groups in the corrected TIMI frame count and in the percent change in end-diastolic volume retained marginal statistical significance.

**MAJOR ADVERSE CARDiac EVENTS AND FUNCTIONAL CAPACITY AT FOLLOW-UP**

In the streptokinase group, one patient underwent surgical revascularization at 2 months and one had reinfarction at 1 month. There was one case of sudden cardiac death in the control group at 4 months. Two patients in the streptokinase group and three patients in the control group underwent PCI owing to hemodynamically significant restenosis at 6 months. All other patients had a functional capacity equivalent to New York Heart Association class I at 6 months.

**DISCUSSION**

In our pilot trial, primary PCI immediately followed by the intracoronary administration of low-dose streptokinase was compared with standard primary PCI without the use of intracoronary streptokinase. Multiple quantitative end points including coronary flow reserve, collateral-flow index, coronary wedge pressure, and coronary diastolic deceleration time were used to evaluate microvascular integrity.\(^{20-22}\) We also measured the index of microvascular resistance, which has been shown to be a useful variable for direct assessment of microcirculatory function.\(^{17,23}\) On the basis of these assessments, the use of intracoronary streptokinase was associated with better perfusion at the microvascular level.

The extent of microvascular dysfunction has been shown to be an important and independent contributor to subsequent changes in left ventricular geometry and performance.\(^{24,25}\) In our study, however, there was at best limited statistical evidence of a benefit to left ventricular size or function on the basis of long-term follow-up in the streptokinase group. The end points with marginal significance may reflect chance associations, given the number of tests performed. Since trends favoring the streptokinase group were detected, it is possible that the study was underpowered for these analyses. The trial was not originally planned to be large enough to detect differences in long-term outcome, and indeed enrollment was terminated early on the basis of the interim data on microvascular perfusion.

The precise mechanisms underlying myocardial malperfusion after the restoration of epicardial blood flow are likely to be multifactorial. The generation of oxygen free radicals, increased myocardial-cell calcium levels, cellular and interstitial edema, endothelial dysfunction, vasoconstriction, and thromboembolism have all been proposed.\(^{2,26}\)

Injury to the endothelium also promotes a procoagulant milieu. Fibrin and platelet aggregates have been found in the coronary microvasculature of patients who have died of acute myocardial infarction.\(^{27}\) In addition to fibrin formation, red-cell and platelet aggregation also contribute to microvascular occlusion and increased resistance in the microvasculature.

It has been shown that streptokinase inhibits red-cell aggregation and reduces platelet aggregation in vitro.\(^{28,29}\) It has also been shown histopathologically, in an open-chest model of anterior descending artery occlusion and reperfusion, that streptokinase reduces congestion at the site of injury and results in improved perfusion of the microvasculature in severely ischemic myocardium to which blood flow has been restored.\(^{30}\) It is therefore reasonable to assume that intracoronary streptokinase, administered immediately after primary PCI, may improve myocardial perfusion through mechanisms that cannot be invoked by distal protection devices.

We chose a 250-kU dose of streptokinase, which we anticipated would be high enough to induce fibrinolysis at the site of injury yet low enough to limit the risk of hemorrhage. At this dose, intracoronary streptokinase should have a concentration at the site of injury that is 50 times that of the standard dose of intravenous streptokinase (1.5 MU), resulting in a concentration in the systemic circulation that is 6 times less than that of the standard dose. In addition, since our protocol specified the administration of streptokinase after the infarct-related artery is opened, the drug would be expected to arrive at the target site much more quickly than with intravenous use.

Several important limitations of our study should be noted. First, because it was a pilot trial, only 41 patients were enrolled. Confirmation of the results with respect to early microvascular perfusion and clarification of the long-term effects on ventricular size and function will require a much larger trial. Second, since there is no single, uniformly accepted method for evaluating coronary microvascular perfusion, it may be argued that the measures used are not sufficiently sensitive or specific for this disease process. We had hoped to increase the reliability of our results by using mul-
Table 2. Invasive and Noninvasive Measures of Microvascular Perfusion, According to Type of Analysis.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th>Analysis of LAD Subgroup†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Streptokinase Group (N = 21)</td>
<td>Control Group (N = 20)</td>
<td>Mean Difference (95% CI)</td>
</tr>
<tr>
<td>Index of microvascular resistance — U</td>
<td>16.29 ± 5.06</td>
<td>32.49 ± 11.04</td>
<td>−16.20 (−21.75 to 10.64)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>10.81 ± 5.46</td>
<td>17.20 ± 7.93</td>
<td>−6.39 (−10.73 to −2.05)</td>
</tr>
<tr>
<td>Systolic</td>
<td>18.24 ± 6.07</td>
<td>33.80 ± 11.00</td>
<td>−15.56 (−21.27 to −9.85)</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>2.01 ± 0.57</td>
<td>1.39 ± 0.31</td>
<td>0.62 (0.35 to 0.93)</td>
</tr>
<tr>
<td>Coronary wedge pressure — mm Hg</td>
<td>18.24 ± 6.07</td>
<td>33.80 ± 11.00</td>
<td>−15.56 (−21.27 to −9.85)</td>
</tr>
<tr>
<td>Pressure-derived collateral-flow index</td>
<td>0.08 ± 0.05</td>
<td>0.17 ± 0.07</td>
<td>−0.09 (−0.13 to −0.06)</td>
</tr>
<tr>
<td>Corrected TIMI frame count</td>
<td>33.65 ± 9.45</td>
<td>34.44 ± 8.26</td>
<td>−0.79 (−6.66 to 5.08)</td>
</tr>
<tr>
<td>immediately after primary PCI</td>
<td>33.65 ± 9.45</td>
<td>34.44 ± 8.26</td>
<td>−0.79 (−6.66 to 5.08)</td>
</tr>
<tr>
<td>2 days after primary PCI</td>
<td>22.52 ± 5.58</td>
<td>31.79 ± 7.58</td>
<td>−9.27 (−13.50 to −5.03)</td>
</tr>
<tr>
<td>6 mo after primary PCI</td>
<td>21.42 ± 4.98</td>
<td>27.62 ± 6.46</td>
<td>−6.20 (−11.00 to −1.39)</td>
</tr>
<tr>
<td>TIMI myocardial blush grade‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>immediately after primary PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>0 or 1 — no. (%)</td>
<td>10 (50)</td>
<td>13 (72)</td>
<td></td>
</tr>
<tr>
<td>2 or 3 — no. (%)</td>
<td>10 (50)</td>
<td>5 (28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days after primary PCI</td>
<td>6 mo after primary PCI</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Total no. of patients</strong></td>
<td>21 19</td>
<td>12 13</td>
<td></td>
</tr>
<tr>
<td>0 or 1 — no. (%)</td>
<td>6 (29) 13 (68)</td>
<td>1 (8) 6 (46)</td>
<td></td>
</tr>
<tr>
<td>2 or 3 — no. (%)</td>
<td>15 (71) 6 (32)</td>
<td>11 (92) 7 (54)</td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic deceleration time in the LAD artery — msec</strong></td>
<td>828±258 360±292</td>
<td>828±258 360±292</td>
<td></td>
</tr>
<tr>
<td><strong>ST-segment resolution — %</strong></td>
<td>68.21±20.13 63.21±14.37</td>
<td>67.55±22.91 51.25±24.40</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. LAD denotes left anterior descending coronary artery, and PCI percutaneous coronary intervention.
† The left anterior descending coronary artery (LAD) subgroup consisted of patients with anterior myocardial infarction (in whom the infarct-related artery was the LAD).
‡ The Thrombolysis in Myocardial Infarction (TIMI) myocardial blush grade was not available for all patients at all time points.
§ Diastolic deceleration time was measured in 14 patients in the intracoronary-streptokinase group and in 16 patients in the control group.
Table 3. Left Ventricular Function at 2 Days and 6 Months and Infarct Size at 6 Months.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Streptokinase Group (N = 21)</th>
<th>Control Group (N = 20)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
<th>Streptokinase Group (N = 21)</th>
<th>Control Group (N = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 days after primary PCI</td>
<td>58.16±17.02</td>
<td>78.65±30.55</td>
<td>-20.48 (-36.38 to 4.59)</td>
<td>0.01</td>
<td>50.81 (31.25 to 66.37)</td>
<td>65.03 (47.76 to 82.30)</td>
<td>0.06</td>
</tr>
<tr>
<td>6 mo after primary PCI</td>
<td>50.64±18.23</td>
<td>83.73±39.32</td>
<td>-33.08 (-56.24 to 9.92)</td>
<td>0.004</td>
<td>36.08 (9.07 to 63.10)</td>
<td>58.68 (25.10 to 92.27)</td>
<td>0.07</td>
</tr>
<tr>
<td>Percent change</td>
<td>-13.27±25.40</td>
<td>12.67±30.75</td>
<td>-25.94 (-46.22 to -5.67)</td>
<td>0.01</td>
<td>-12.32 (-47.47 to -22.83)</td>
<td>15.30 (-28.40 to 59.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 days after primary PCI</td>
<td>119.88±23.36</td>
<td>137.75±36.82</td>
<td>-17.86 (-37.24 to 1.51)</td>
<td>0.07</td>
<td>111.22 (88.52 to 133.91)</td>
<td>118.53 (93.35 to 143.71)</td>
<td>0.50</td>
</tr>
<tr>
<td>6 mo after primary PCI</td>
<td>115.70±29.67</td>
<td>150.13±49.28</td>
<td>-34.42 (-63.39 to 5.46)</td>
<td>0.02</td>
<td>92.72 (59.11 to 126.33)</td>
<td>118.77 (76.98 to 160.56)</td>
<td>0.09</td>
</tr>
<tr>
<td>Percent change</td>
<td>-4.60±22.01</td>
<td>11.90±23.50</td>
<td>-16.51 (-32.95 to 0.07)</td>
<td>0.04</td>
<td>-11.19 (-37.95 to 15.58)</td>
<td>14.97 (-18.31 to 48.24)</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 days after primary PCI</td>
<td>51.52±10.76</td>
<td>44.51±12.40</td>
<td>7.00 (-0.31 to 14.33)</td>
<td>0.06</td>
<td>54.25 (46.95 to 61.55)</td>
<td>47.96 (39.86 to 56.06)</td>
<td>0.08</td>
</tr>
<tr>
<td>6 mo after primary PCI</td>
<td>56.18±10.69</td>
<td>46.19±12.21</td>
<td>9.99 (1.72 to 18.26)</td>
<td>0.02</td>
<td>57.68 (45.88 to 69.47)</td>
<td>51.56 (36.90 to 66.23)</td>
<td>0.24</td>
</tr>
<tr>
<td>Percent change</td>
<td>14.37±31.14</td>
<td>3.46±19.02</td>
<td>10.9 (-7.7 to 29.5)</td>
<td>0.24</td>
<td>5.97 (-27.32 to 39.26)</td>
<td>2.71 (-37.75 to 43.16)</td>
<td>0.82</td>
</tr>
<tr>
<td>Infarct size at 6 mo (%)</td>
<td>23.1±13.37</td>
<td>37.05±13.84</td>
<td>-14.05 (-23.27 to -4.83)</td>
<td>0.005</td>
<td>27.84 (14.35 to 41.32)</td>
<td>37.28 (21.57 to 52.99)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Left ventricular volumes were determined with the use of echocardiography. Echocardiography data were collected 2 days after primary PCI for all patients but 6 months after primary PCI for only the 17 patients in the streptokinase group and the 15 patients in the control group with less than 70% stenosis in the stented segment on angiography, to avoid the confounding effect of restenosis of the infarct-related artery; percent changes were based on the 17 and 15 patients for whom data were available at each time point. Infarct size was determined with the use of single-photon-emission computed tomography (SPECT), which was performed in 18 patients in each of the two groups, and is expressed as a percentage of the total area of the myocardium. CI denotes confidence interval, PCI percutaneous coronary intervention, and LVEF left ventricular ejection fraction.
multiple measures. Third, although the analysis of coronary hemodynamic measurements was blinded, the measurements were made by angiographers who were aware of the group assignments, so it is not possible to rule out entirely some element of investigator bias in our findings.

Finally, although we did not observe an increase in the rate of bleeding complications in the stentekine group, the potential risk of adding even a low dose of a thrombolytic agent to an anti-thrombotic regimen that already includes aspirin, clopidogrel, and tirofiban must be considered. In the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) trial, the use of full-dose tenecteplase just before primary PCI was associated with an increased risk of intracranial hemorrhage. In a smaller trial of PCI facilitated with the use of abciximab, the addition of half-dose reteplase was not associated with a significant reduction in the rate of subsequent ischemic events. Therefore, it appears that thrombolytic agents administered before primary PCI confer no discernible benefit at low doses and increase risk at high doses. Although the use of thrombolysis after primary PCI may have distinct effects, the implications of these related trials should be kept in mind.

In conclusion, in our pilot evaluation, primary PCI followed by the administration of low-dose intracoronary streptokinase immediately after the procedure was associated with improved microvascular perfusion, but not with long-term improvement in ventricular size or function, as compared with primary PCI alone. Confirmation of the improvement in microvascular perfusion and clarification of the long-term benefit, if any, will require a much larger trial.

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REFERENCES


Age at Surgery for Undescended Testis and Risk of Testicular Cancer

Andreas Pettersson, M.D., Lorenzo Richiardi, M.D., Ph.D., Agneta Nordenskjold, M.D., Ph.D., Magnus Kaijser, M.D., Ph.D., and Olof Akre, M.D., Ph.D.

ABSTRACT

BACKGROUND
Undescended testis, which is a risk factor for testicular cancer, is usually treated surgically, but whether the age at treatment has any effect on the risk is unclear. We studied the relation between the age at treatment for undescended testis and the risk of testicular cancer.

METHODS
We identified men who underwent orchiopexy for undescended testis in Sweden between 1964 and 1999. Cohort subjects were identified in the Swedish Hospital Discharge Register and followed for the occurrence of testicular cancer through the Swedish Cancer Registry. Vital statistics and data on migration status were taken from the Register of Population and Population Changes for the years 1965 through 2000. We estimated the relative risk of testicular cancer using Poisson regression of standardized incidence ratios, comparing the risk in the cohort with that in the general population. We also analyzed the data by means of Cox regression, using internal comparison groups.

RESULTS
The cohort consisted of 16,983 men who were surgically treated for undescended testis and followed for a total of 209,984 person-years. We identified 56 cases of testicular cancer during follow-up. The relative risk of testicular cancer among those who underwent orchiopexy before reaching 13 years of age was 2.23 (95% confidence interval [CI], 1.58 to 3.06), as compared with the Swedish general population; for those treated at 13 years of age or older, the relative risk was 5.40 (95% CI, 3.20 to 8.53). The effect of age at orchiopexy on the risk of testicular cancer was similar in comparisons within the cohort.

CONCLUSIONS
Treatment for undescended testis before puberty decreases the risk of testicular cancer.
Undescended Testis, or Cryptorchidism, which occurs in 2 to 5% of boys born at term, is one of the most common congenital abnormalities. Cryptorchidism is associated with impaired fertility and is a risk factor for testicular cancer. Among men who have had undescended testis, the risk of cancer is increased two to eight times, and 5 to 10% of all men with testicular cancer have a history of cryptorchidism. However, it is unknown whether cryptorchidism and testicular cancer have a common cause, or whether cryptorchidism is in itself a cause of testicular cancer.

Testes that are undescended at birth may descend spontaneously during early life, but seldom thereafter. By 12 months of age, about 1% of all boys have cryptorchidism. Treatment for persistent cryptorchidism is generally orchiopexy, a surgical correction in which the testicle is placed and fixed in the scrotum. There is evidence that postnatal germ-cell development deteriorates in the undescended testis after the first year, and perhaps for this reason, the risk of infertility increases with age. The recommended age for orchiopexy has therefore been successively lowered, and the procedure is now recommended for patients younger than 2 years old and even as young as 6 months old.

The question of whether the age at treatment has any effect on the risk of testicular cancer is controversial. According to the predominant view, the mechanism leading to testicular cancer is present before birth and the risk of cancer is largely determined in utero or early in life. If this view is correct, then the age at surgical correction should not be related to the rate of testicular cancer. Some studies suggest, however, that orchiopexy at an early age decreases the risk of testicular cancer. Even so, most of these studies used retrospectively collected data, and all of them were too small to produce conclusive results. We investigated the risk of testicular cancer according to the age at orchiopexy in a cohort of almost 17,000 Swedish men who were surgically treated for cryptorchidism between 1964 and 1999.

**METHODS**

**THE REGISTRIES**

We used data from the Swedish Hospital Discharge Register to assemble the study cohort, which was followed from 1965 to 2000 through linkage to the Swedish Cancer Registry and the Register of Population and Population Changes. Linkage was performed on the basis of the national registration number, a unique personal identifier referred to in all hospital records and official registries in Sweden.

In 1964, the Swedish National Board of Health and Welfare initiated the Hospital Discharge Register, which compiles data on individual discharges from Swedish public hospitals. Virtually all patients in Sweden are treated at public hospitals, making the Discharge Register representative of hospitalizations in the Swedish population. Each record contains medical and administrative data, including the dates of admission and discharge, surgical procedures performed, the main diagnosis at discharge, and up to five contributory diagnoses. The surgical procedures were coded from 1964 to 1996 according to the *Swedish Classification of Operations and Major Procedures*, first through sixth editions, and from 1997 onward according to the *Classification of Surgical Procedures, 1997 edition*. The diagnoses at discharge were coded according to the Swedish version of the *International Classification of Diseases*, with the 7th revision (ICD-7) used for the years 1964 through 1968, the 8th revision (ICD-8) for 1969 through 1986, the 9th revision (ICD-9) for 1987 through 1996, and the 10th revision (ICD-10) thereafter.

In 1964, the Discharge Register covered 6 of the 26 health care regions in Sweden. Gradually, more hospitals were included, and by 1975, 16 health care regions were fully covered (including the three largest cities in Sweden: Stockholm, Gothenburg, and Malmö). Since 1987, the registry has covered all hospitals in Sweden.

The Swedish Cancer Registry was established in 1958 and obtains mandatory reported data from both clinicians and pathologists on all newly diagnosed malignant neoplasms. Information on the site and histopathological features of the tumors is recorded. The registry is estimated to be more than 95% complete. The Register of Population and Population Changes contains the official Swedish population data, including dates of death and migration; the data have been available since 1960.

**THE COHORT**

We confined our study cohort to all subjects in the Discharge Register who had received a diagnosis of cryptorchidism (main or contributory dis-
charge diagnosis ICD-7 code 757.00, ICD-8 code 752.10, ICD-9 code 752F, or ICD-10 code Q53.0, Q53.1, Q53.2, or Q53.9) between January 1964 and December 1999 and who had been treated with orchiopexy (surgical procedure code 6790, KFH00, or KFH10) before 20 years of age. The restriction to those who underwent surgery before 20 years of age minimized the influence of selection bias due to, for instance, referral of men seeking treatment for infertility to the urology department.

One subject in whom testicular cancer had already been diagnosed, 205 subjects who emigrated from Sweden after orchiopexy and did not immigrate back to Sweden before the beginning of their follow-up, and 12 subjects with conflicting information on sex or date of orchiopexy were excluded from the study cohort, leaving 16,983 subjects for the analysis. Among 2667 (15.7%) subjects who were surgically treated for cryptorchidism more than once, we used the date of the last admission as the index date of orchiopexy.

The study was approved by the ethics committee of the Karolinska Institute. Informed consent was not required.

**Statistical Analysis**

The members of the cohort were followed from 15 years of age or the age at orchiopexy plus 1 year, whichever occurred later, to the date of diagnosis of germ-cell testicular cancer (ICD-7 code 178), the age of 55, emigration, death, or December 31, 2000, whichever occurred first. The first year after orchiopexy was excluded to reduce the risk of selection bias. The germ-cell testicular cancers we included were seminomas and nonseminomas, the latter encompassing teratomas, choriocarcinomas, yolk-sac tumors, embryonal carcinomas, and mixed germ-cell tumors.

We estimated the relative risk of testicular cancer by calculating the standardized incidence ratio (the observed number of cases of testicular cancer divided by the expected number). Expected numbers of testicular cancer were based on the 5-year age- and period-specific rates in the Swedish general population. We estimated 95% confidence intervals (CIs) assuming a Poisson distribution. Analyses were also stratified according to age at orchiopexy and calendar period of orchiopexy. In categorizing age at orchiopexy, we focused on the ages around puberty. Categories are therefore smaller for the group between 10 and 15 years of age and larger for ages before and after. Thirteen years of age was set a priori as the cutoff for analyses of surgery before and after puberty.

We used Cox regression analysis, with age as the temporal axis, to estimate the hazard ratio for testicular cancer associated with age at orchiopexy in comparisons within the cohort. Covariates included in the model were the calendar period of follow-up (1965 to 1990, 1991 to 1995, and 1996 to 2000), calendar period of orchiopexy, and region where the orchiopexy was performed (two categories: the three largest cities in Sweden and the rest of Sweden). There is collinearity among birth cohort, age at orchiopexy, and calendar period of orchiopexy (e.g., a child operated on at 5 years of age in 1970 must have been born in 1964 or 1965).

To analyze the effect of age at orchiopexy adjusted by calendar period of orchiopexy, we therefore used only three categories for the latter variable (1964 to 1969, 1970 to 1974, and 1975 to 1999), assuming no period effect after 1974. Both visual inspection of a graph (with the log of the cumulative hazard on the y axis and the log of the survival time on the x axis) and a formal test based on Schoenfeld residuals (\(P = 0.68\)) indicated that the proportional-hazard assumption was met. There was no evidence of interaction between the calendar period of follow-up and the effect of age at orchiopexy.

We also conducted a sensitivity analysis, restricting the cohort to men born between 1964 and 1980, among whom the estimate of the effect of age at orchiopexy could not be biased by the lack of information about orchiopexy before 1964 (when the Discharge Register was established) or by the termination of the follow-up at 2000.

**Results**

The cohort consisted of 16,983 men who were surgically treated for cryptorchidism and followed for a mean (±SD) period of 12.4±7.4 years, with a total of 209,984 person-years at risk. For 679 of the subjects, follow-up ended before December 31, 2000, because of a diagnosis of testicular cancer (56), emigration (436), reaching the age of 55 years (5), or death (182). The overall mean age at orchiopexy was 8.6±3.5 years, and the median age was 8.5 years. Table 1 lists the main characteristics of the cohort.

We identified 56 cases of testicular cancer during the follow-up period, as compared with 20 expected cases, resulting in a standardized inci-
The standardized incidence ratio of testicular cancer among those operated on before the age of 13 years was 2.23 (95% CI, 1.58 to 3.06), whereas it was 5.40 (95% CI, 3.20 to 8.53) for those treated at age 13 or later (Table 2). There were no significant differences in risk between groups below (P = 0.81) or above (P = 0.68) the age of 13 years. The proportion of men who were 13 years of age or older at orchiopexy declined from 27.3% in the beginning of the study period to 5.4% during the late 1980s (Table 3).

Figure 1 shows the standardized incidence ratios for testicular cancer according to the calendar period of orchiopexy among men who underwent the surgery before the age of 13 years and among those who were surgically treated when they were 13 years or older. The standardized incidence ratio for all men in the cohort decreased from 8.64 (95% CI, 4.47 to 15.10) among those operated on between 1964 and 1969 to 3.29 (95% CI, 1.95 to 5.21) for those operated on between 1970 and 1974, and it did not vary much after that. The relative difference between the standardized incidence

Table 1. Characteristics of the Cohort of Men Who Underwent Surgery for Cryptorchidism.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men Who Underwent Surgery</th>
<th>Person-Years of Follow-Up</th>
<th>Men with Testicular Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>16,983 (100)</td>
<td>209,984 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Age at orchiopexy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 yr</td>
<td>718 (4.2)</td>
<td>4,395 (2.1)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>3–6 yr</td>
<td>5,139 (30.3)</td>
<td>47,303 (22.5)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>7–9 yr</td>
<td>5,047 (29.7)</td>
<td>61,172 (29.1)</td>
<td>14 (25.0)</td>
</tr>
<tr>
<td>10–12 yr</td>
<td>4,417 (26.0)</td>
<td>65,339 (31.1)</td>
<td>15 (26.8)</td>
</tr>
<tr>
<td>13–15 yr</td>
<td>1,217 (7.2)</td>
<td>22,884 (10.9)</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>16–19 yr</td>
<td>445 (2.6)</td>
<td>8,891 (4.2)</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>Calendar year of orchiopexy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1964–1969</td>
<td>542 (3.2)</td>
<td>14,575 (6.9)</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>1970–1974</td>
<td>2,326 (13.7)</td>
<td>50,185 (23.9)</td>
<td>18 (32.1)</td>
</tr>
<tr>
<td>1975–1979</td>
<td>3,780 (22.3)</td>
<td>63,030 (30.0)</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>1980–1984</td>
<td>4,714 (27.8)</td>
<td>53,281 (25.4)</td>
<td>10 (17.9)</td>
</tr>
<tr>
<td>1985–1989</td>
<td>3,522 (20.7)</td>
<td>22,464 (10.7)</td>
<td>5 (8.9)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>1,823 (10.7)</td>
<td>6,002 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>1995–1999</td>
<td>276 (1.6)</td>
<td>447 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1963 or earlier</td>
<td>2,129 (12.5)</td>
<td>52,038 (24.8)</td>
<td>27 (48.2)</td>
</tr>
<tr>
<td>1964–1969</td>
<td>3,524 (20.8)</td>
<td>64,394 (30.7)</td>
<td>14 (25.0)</td>
</tr>
<tr>
<td>1970–1974</td>
<td>3,855 (22.7)</td>
<td>50,866 (24.2)</td>
<td>10 (17.9)</td>
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<tr>
<td>1975–1979</td>
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<td>31,293 (14.9)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>1980–1985</td>
<td>3,788 (22.3)</td>
<td>11,393 (5.4)</td>
<td>1 (1.8)</td>
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<td>Type of cancer</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>23 (41.1)</td>
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<tr>
<td>Nonseminoma</td>
<td>33 (58.9)</td>
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<tr>
<td>Region*</td>
<td></td>
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<tr>
<td>Urban</td>
<td>5,468 (32.2)</td>
<td>71,458 (34.0)</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Nonurban</td>
<td>11,515 (67.8)</td>
<td>138,526 (66.0)</td>
<td>39 (69.6)</td>
</tr>
</tbody>
</table>

* The urban category includes Sweden’s three largest cities: Stockholm, Gothenburg, and Malmö. Percentages may not total 100 because of rounding.
ratios for those who underwent surgery before the age of 13 years and those in whom surgery was performed at or after the age of 13 years was close to 2 in most of the calendar periods (Fig. 1).

The within-cohort analysis of the effects of age at orchiopexy on the risk of testicular cancer were consistent with the findings obtained when the rates of testicular cancer in the study cohort were compared with Swedish national rates (Fig. 2). The adjusted hazard ratio for testicular cancer among men who were 13 years of age or older when surgery was performed, as compared with those who were younger at the time of treatment was 1.99 (95% CI, 1.00 to 3.95). Analyses restricted to men born between 1964 and 1980 revealed a hazard ratio of 3.56 (95% CI, 1.34 to 9.47), based on 6 cases in which surgery was performed at 13 years of age or later and 23 cases in which surgery was performed at an earlier age.

**Discussion**

In this cohort study of 16,983 men who were surgically treated for cryptorchidism, we found that the risk of testicular cancer among men who were treated at 13 years of age or older was approximately twice that among men who underwent orchiopexy before the age of 13. The results indicate that early, rather than late, surgical treatment can best prevent testicular cancer in boys with cryptorchidism. The results also suggest that the ectopic position of the testis is a factor in the development of testicular cancer.

In our large cohort study, the use of strict criteria for identification of cohort members — registration with both diagnosis and surgical procedure — reduced the likelihood of misclassification of cryptorchidism. By starting follow-up 1 year after the date of surgery and by restricting the cohort to men who had been treated before reaching 20 years of age, the risk of including cohort members who already had testicular cancer should have been minimized. Moreover, use of the nationwide cancer registry to ascertain outcome virtually ensured complete follow-up.

In principle, the gradual inclusion of health care regions in the Discharge Register could have biased the results. However, the incidence of testicular cancer in Sweden is fairly homogeneous, and in analyses with an internal comparison group, in which we could adjust for the region, estimates of risk were similar to those in the analysis in which the general population was used as the comparison group. For this reason, it is unlikely that such a bias had any major influence on the results.

The strong effect of the calendar period of orchiopexy on the risk of testicular cancer (Fig. 1) suggests that unknown risk factors correlated with calendar time affect the risk estimates. The effect of age at orchiopexy on the risk of testicular cancer was, however, essentially constant over calendar periods. Consequently, it is unlikely that the factors underlying the effect of the calendar period of orchiopexy can explain the effect of age at orchiopexy on the risk of testicular cancer.

Other studies have examined the age at orchiopexy in relation to the risk of testicular cancer. Most of these investigations were case-control studies with small samples. Several suggest that the risk of testicular cancer increases with age at treatment, with men treated after the age of 10 to 15 years at greatest risk. In our study,

| Table 2. Standardized Incidence Ratio for Testicular Cancer According to the Age at Orchiopexy among Men 15 to 55 Years of Age between 1965 and 2000.* |
|---------------------------------|------------------|------------------|
| Age at Orchiopexy | No. of Men with Testicular Cancer | Standardized Incidence Ratio (95% CI) |
| All ages | 56 | 2.75 (2.08–3.57) |
| 0–6 yr | 9 | 2.02 (0.93–3.84) |
| 7–9 yr | 14 | 2.35 (1.28–3.94) |
| 10–12 yr | 15 | 2.27 (1.27–3.74) |
| 13–15 yr | 12 | 5.06 (2.61–8.84) |
| 16–19 yr | 6 | 6.24 (2.29–13.58) |
| <13 yr | 38 | 2.23 (1.58–3.06) |
| ≥13 yr | 18 | 5.40 (3.20–8.53) |

* The Swedish general population was used as the comparison group.

| Table 3. Proportion of Men in the Cohort Who Were Treated at 13 Years of Age or Older. |
|---------------------------------|------------------|
| Year* | Men Treated at 13 Years of Age or Older % |
| 1964–1969 | 27.3 |
| 1970–1974 | 14.8 |
| 1975–1979 | 10.8 |
| 1980–1984 | 7.2 |
| 1985–1989 | 5.4 |

* Data are not shown for later years because day-surgery orchiopexies were introduced in Sweden in the early 1990s.
that may not be associated with testicular cancer, such as spontaneously descending testes or retractile testis. To observe the risk pattern we found, however, 25% of the patients treated before 13 years of age would have to have had nondescending cryptorchidism, as compared with 100% of the patients treated at 13 years of age or older. It therefore seems that the ectopic location of the testis at puberty explains the increase in risk at age 13. It is also believed that the risk of germ-cell cancer of the testis is largely determined in utero. The results of our study are partly consistent with this hypothesis, since the risk was increased in the entire cohort, regardless of the age at surgical treatment. Our results, however, suggest that puberty, here defined arbitrarily as beginning at the age of 13 years, is another crucial event in testicular carcinogenesis.

Some studies have indicated that the risk of testicular cancer in the contralateral testis is increased in men with unilateral cryptorchidism, although to a lesser extent than in the undescended testis. We could not assess the risk of cancer in the contralateral testis, nor could we assess the effect of age at unilateral orchiopexy on the risk of cancer in the contralateral testis, because information on laterality is not available in the registries used in our study.

Despite unambiguous recommendations for early treatment, a proportion of boys with cryptorchidism are still left untreated until much later in life. Sweden has a well-developed nationwide system to screen for cryptorchidism at several points in life, starting with neonatal care and continuing at child health care centers and at school. Since all checkups are free, attendance at these clinics should have been high. Yet in our cohort, approximately 5% of the orchiopexies in the late 1980s were performed at the age of 13 to 19 years. This proportion seems to have remained unchanged ever since. According to 2005 data from the Swedish National Board of Health and Welfare, about 6% of the orchiopexies in Sweden were performed at the age of 13 years or older. In the United Kingdom and the Netherlands, in the late 1990s, about 10 to 20% of the orchiopexies were performed at the age of 13 years or older.

According to the Swedish Cancer Registry, the cumulative incidence of testicular cancer until the age of 54 years in Sweden in 2004 was approximately 0.5%. Given the relative risks in our study, we calculated that 69 boys would need to be treated before 13 years of age (instead of at or after

Figure 1. Standardized Incidence Ratio for Testicular Cancer According to Calendar Period of Orchiopexy among Men Treated before the Age of 13 Years and Those Treated When They Were 13 Years or Older.
The general population in Sweden was used as the comparison group. I bars denote the upper and lower limits of the 95% confidence intervals.

Figure 2. Hazard Ratio for Testicular Cancer According to Age at Orchiopexy.
A within-cohort comparison was used. I bars denote the upper and lower limits of the 95% confidence intervals.
that age) to avoid one case of testicular cancer in Sweden before the age of 55 years.

In summary, our results indicate that age at orchiopexy has an effect on the risk of testicular cancer in boys with an undescended testicle; the risk among those treated at 13 years of age or older was twice the risk among those who were treated at younger ages.

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REFERENCES


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Long-Term Effect of Diabetes and Its Treatment on Cognitive Function

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group*

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*Participants in the DCCT/EDIC Study Research Group are listed in the Appendix.


ABSTRACT

BACKGROUND
Long-standing concern about the effects of type 1 diabetes on cognitive ability has increased with the use of therapies designed to bring glucose levels close to the non-diabetic range and the attendant increased risk of severe hypoglycemia.

METHODS
A total of 1144 patients with type 1 diabetes enrolled in the Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study were examined on entry to the DCCT (at mean age 27 years) and a mean of 18 years later with the same comprehensive battery of cognitive tests. Glycated hemoglobin levels were measured and the frequency of severe hypoglycemic events leading to coma or seizures was recorded during the follow-up period. We assessed the effects of original DCCT treatment-group assignment, mean glycated hemoglobin values, and frequency of hypoglycemic events on measures of cognitive ability, with adjustment for age at baseline, sex, years of education, length of follow-up, visual acuity, self-reported sensory loss due to peripheral neuropathy, and (to control for the effects of practice) the number of cognitive tests taken in the interval since the start of the DCCT.

RESULTS
Forty percent of the cohort reported having had at least one hypoglycemic coma or seizure. Neither frequency of severe hypoglycemia nor previous treatment-group assignment was associated with decline in any cognitive domain. Higher glycated hemoglobin values were associated with moderate declines in motor speed (P=0.001) and psychomotor efficiency (P<0.001), but no other cognitive domain was affected.

CONCLUSIONS
No evidence of substantial long-term declines in cognitive function was found in a large group of patients with type 1 diabetes who were carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycemia. (ClinicalTrials.gov number, NCT00360893.)
OVER TIME, IMPROVING GLYCEMIC CONTROL decreases the risk of microvascular, peripheral neuropathic, and macrovascular complications of type 1 diabetes. However, it is unclear whether type 1 diabetes and its treatment have substantial effects on the structure and function of the central nervous system. The widespread use of intensive therapies designed to achieve glycemic control near the nondiabetic range and the attendant increased risk of severe hypoglycemia have elevated concern about the effects of hypoglycemia on the central nervous system.

The Diabetes Control and Complications Trial (DCCT) incorporated a comprehensive battery of cognitive tests to evaluate the effect of diabetes treatment and recurrent hypoglycemic events on cognitive ability. At an average of 6.5 years of follow-up, no untoward effects were associated with either treatment type (conventional or intensive) or with the number of severe hypoglycemic episodes during the DCCT. However, the DCCT involved a short follow-up of adolescent and young adult patients (mean age, 27 years) who had had relatively few hypoglycemic events. Although these initial findings were promising, longer-term follow-up was needed to determine whether the increase by a factor of three in the frequency of severe hypoglycemia among patients receiving intensive therapy during the DCCT adversely affected cognitive ability over time. Moreover, a longer-term study would allow for an investigation of the potential effects on cognition of recurrent, severe hypoglycemia during the post-DCCT follow-up period; of persistent differences in glycemic control, as indicated by the glycated hemoglobin value; and of the increased age of the cohort members and the increased duration of their diabetes.

To address these questions, we repeated the cognitive evaluation 12 years after the end of the DCCT as part of the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study. Thus, the average total follow-up time was 18 years. The longitudinal follow-up of this carefully characterized cohort with type 1 diabetes addressed three specific questions: Was assignment to intensive versus conventional therapy during the DCCT associated with differences in cognitive decline over the 18-year follow-up period? Is a history of severe hypoglycemic events leading to coma and seizures associated with cognitive decline? Is the level of long-term glycemic control, as measured by glycated hemoglobin values, associated with cognitive decline?

METHODS

PATIENTS

Between 1983 and 1989, a total of 1441 patients from 13 through 39 years of age with type 1 diabetes were enrolled in the DCCT. The DCCT study population consisted of two cohorts. Patients in the primary-prevention cohort had received a diagnosis of diabetes 1 to 5 years previously, had no retinopathy, and had a urinary albumin excretion rate of less than 40 mg per 24 hours. The secondary-intervention cohort consisted of patients who had had diabetes for 1 to 15 years, had nonproliferative retinopathy ranging from very mild to moderate, and had a urinary albumin excretion rate of 200 mg per 24 hours or less at baseline.

A total of 711 patients were randomly assigned to intensive therapy. Intensive therapy consisted of three or more insulin injections daily or subcutaneous infusion of insulin with an external pump, guided by frequent self-monitoring of blood glucose levels. The target preprandial blood glucose level was between 3.9 and 6.7 mmol per liter (70 and 120 mg per deciliter), the target glycated hemoglobin value (measured monthly) was within the nondiabetic range (<6.0%), and a goal of therapy was to prevent severe hypoglycemia. The remaining 730 patients were assigned to conventional therapy. These patients received one or two insulin injections daily; there were no target blood glucose levels, and the therapeutic goal was freedom from symptoms of hyperglycemia and from frequent or severe hypoglycemia.

During the 6.5-year DCCT follow-up, the median glycated hemoglobin values of the two treatment groups were maintained at a separation of 1.9 percentage points (7.1% in the intensive-treatment group and 9.0% in the conventional-treatment group). At the end of the DCCT, in 1993, intensive therapy was recommended for all patients, since it had been shown to be highly effective in reducing long-term complications of diabetes. Patients in the conventional-treatment group were given training in aspects of intensive therapy and were then returned to their own health care providers for diabetes care. In 1994, a total of 1375 (96%) of the 1428 surviving members volunteered to participate in the EDIC observational follow-up.
study. As previously reported, between-group differences in the median glycated hemoglobin values narrowed during the 12 years of the EDIC follow-up study to 0.2 percentage point (8.0% in the group that had previously received intensive treatment vs. 8.2% in the group previously receiving conventional treatment, *P* = 0.03). In 2004, of the surviving eligible participants, 1144 (85%) were reevaluated with the cognitive-test battery.

**Cognitive-Test Protocol**

Cognitive testing, as originally described for the DCCT, was conducted at each site by personnel who were trained and certified by the DCCT/EDIC Central Neuropsychological Coding Unit. The test protocol, which required 4 to 5 hours to complete, included the following widely used, well-validated tests that were administered initially during the DCCT: five subtests (Similarities, Digit Span, Digit Symbol, Block Design, and Object Assembly) from the Wechsler Adult Intelligence Scale, four subtests (Category, Tactual Performance, Trail Making, and Finger Tapping) from the Halstead–Reitan Neuropsychological Test Battery, the Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale, the Digit Vigilance Test, the Grooved Pegboard Test, the Verbal Fluency Test, the Four-Word Short-Term Memory Test, the Symbol-Digit Learning Test, and the Embedded Figures Test. The tests were administered in a fixed order. Capillary blood glucose levels were monitored immediately before the testing and at its midpoint to rule out the presence of hypoglycemia during testing. If a patient was found to have a blood glucose level at or below 3.9 mmol per liter (70 mg per deciliter), testing was stopped, the patient was given a snack, and after a wait of at least 15 minutes, testing was resumed when the reading returned to at least 5.0 mmol per liter (90 mg per deciliter).

The tests were scored by technicians at the Central Neuropsychological Coding Unit who were unaware of treatment assignment and other biomedical variables. The results were sent to the Data Coordinating Center, where the data were entered, verified, and edited for out-of-range values and other errors.

The compliance and performance of the patients during the testing session were rated systematically by the personnel administering the cognitive assessment. Information obtained from the patients was rated as “mostly accurate” to “completely accurate” for 97% of the patients. The testing staff also reported that 99% of the patients were “somewhat willing” to “very willing” to try their best throughout the testing session and that 94% of the patients had a “clear understanding” of the test instructions.

**Cognitive Domains**

During the DCCT, 24 test variables had been chosen a priori to be of particular diagnostic value when applied to patients with type 1 diabetes. For each of these 24 test variables, a standardized *z* score was calculated, with the mean and standard deviation from the baseline assessment of the DCCT cohort used as references. These standardized scores provided a unit-free measurement of the relative improvement (positive sign) or deterioration (negative sign) in performance as compared with the total group at baseline. To reduce the number of comparisons, the 24 standardized scores were grouped into eight cognitive domains consistent with standard neuropsychological assessment strategies. For each domain, the simple average of the standardized scores was used to represent the change from baseline, with equal weight assigned to each test.

**Biomedical Evaluations**

During the EDIC study, each patient underwent an annual examination that involved history taking, physical examination, an electrocardiogram, and laboratory tests, including tests for serum creatinine and glycated hemoglobin levels; the examination was conducted by the same methods used during the DCCT. As part of the history, the patients reported the presence of sensory symptoms of peripheral neuropathy. At entry to the DCCT, potential subjects were excluded if they had symptomatic sensory neuropathy. Data from the year in which cognitive testing was performed were used to characterize the level of symptomatic neuropathy at the time of the reevaluation. A criterion for inclusion in the DCCT was a best corrected visual acuity of 20/25 or better for the primary-prevention cohort and 20/32 or better for the secondary-intervention cohort. Best corrected visual acuity was measured at 4-year intervals during the EDIC study. The results of the visual acuity examination closest to the date of cognitive reevaluation were used to characterize the level of visual acuity at the time of cognitive reevaluation. Fast-
ing lipid profiles were determined and 4-hour urine collections for measurement of albumin excretion and creatinine clearance rates were performed in alternate years during the EDIC study. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, previously documented hypertension, or the use of antihypertensive agents. Hypercholesterolemia was defined as a serum level of low-density lipoprotein (LDL) cholesterol of at least 130 mg per deciliter (3.4 mmol per liter) or the use of lipid-lowering agents. Renal insufficiency was defined as a centrally measured serum creatinine level of at least 2.0 mg per deciliter (177 μmol per liter), treatment with dialysis, or renal transplantation.

Glycated hemoglobin values were measured in a central laboratory by high-performance liquid chromatography quarterly during the DCCT and annually during the EDIC study. The time-weighted mean glycated hemoglobin value during the period of the DCCT and the 12 years of the EDIC study was computed, with each DCCT value weighted by one quarter of a year and each EDIC study value weighted by 1 year.

**Psychiatric Symptoms**

Psychiatric symptoms were assessed with the Symptom Checklist-90-Revised, which was administered annually during the DCCT and once during the EDIC study in the same year that the cognitive testing was performed. For this report, the depression scale was used to assess the effects of mood state on cognitive function.

**Definition of Severe Hypoglycemia**

During the DCCT, severe hypoglycemia was defined as any event, including seizure or coma, that required the assistance of another person and in which the blood glucose level was less than 2.8 mmol per liter (50 mg per deciliter) or the symptoms were subsequently reversed by oral carbohydrate, injected glucagon, or intravenous glucose. At quarterly visits, study coordinators asked about the occurrence of hypoglycemia since the last visit, and all such events were reported to the Data Coordinating Center as soon as possible after their occurrence. Twenty-seven percent of severe hypoglycemic episodes involved coma or seizure. During the EDIC study, severe hypoglycemic events that occurred in the 3 months before the annual visit were documented on the annual history form, and further details surrounding these events were recorded. For the purposes of this article, severe hypoglycemic events are limited to those leading to coma, seizure, or both.

**Statistical Analysis**

Demographic and clinical characteristics were compared with the use of the Wilcoxon rank-sum test to evaluate the differences between the treatment groups in ordinal and numeric variables. The contingency chi-square test was used for categorical variables; when the sample size was small, Fisher’s exact test was used. Separate analysis-of-covariance models were used to assess the effects of treatment group (intensive vs. conventional), mean glycated hemoglobin values stratified according to thirds (<7.4%, 7.4 to 8.8%, or >8.8%), and frequency of severe hypoglycemia (zero, one to five, or more than five reported events) on the standardized quantitative score for each of the eight cognitive domains. Each model was adjusted for age at baseline, sex, years of education, length of follow-up, visual acuity, self-reported sensory loss due to peripheral neuropathy, and (to control for the effects of practice) the number of cognitive tests taken during the interval since the start of the DCCT. The results are presented as the average increase or decrease in the standardized score from the DCCT baseline within or between groups or the change per unit in a quantitative covariate. Nominally significant results (P<0.01) are reported.

**Results**

Table 1 presents the characteristics of the cohort at baseline and at the 18-year follow-up. There were no statistically significant differences between the two treatment groups at baseline. At EDIC study year 12, the age of the patients ranged from 29 to 62 years, with a mean (±SD) of 45.7±6.8 years. The only statistically significant difference between the treatment groups was in the percentage of patients with retinopathy (89% in the intensive-treatment group and 97% in the conventional-treatment group, P<0.001), reflecting the effects of previous DCCT interventions. By year 12 of the EDIC study, 3 patients (1 in the intensive-treatment group and 2 in the conventional-treatment group) had a history of stroke, a decrease in vision had occurred in 5 patients (1 in the intensive-treatment group and 4 in the conventional-treatment group)
Table 1. Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At Entry into DCCT (1983–1989)</th>
<th>At Year 12 of EDIC Study (2005)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Intensive Treatment (N=588)</td>
<td>Conventional Treatment (N=556)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>49</td>
<td>45</td>
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<td>White race (%)†</td>
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<td>96</td>
</tr>
<tr>
<td>Mean age (yr)</td>
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<tr>
<td>Adult (%)‡</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Occupation (%)</td>
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<td>33</td>
</tr>
<tr>
<td>Unemployed or retired</td>
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<td>&lt;1</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
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<tr>
<td>Glycated hemoglobin (%)¶</td>
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<td>9.0±1.6</td>
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<tr>
<td>Visual acuity ≥20/40 (%)‖</td>
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<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy (%)**</td>
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<td>14</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<tr>
<td>Systolic</td>
<td>113±12</td>
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<tr>
<td>Diastolic</td>
<td>72±9</td>
<td>73±9</td>
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<tr>
<td>Treated hypertension (%)</td>
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<td>ND</td>
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<tr>
<td>Lipids (mg/dl)††</td>
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</tr>
<tr>
<td>Total cholesterol</td>
<td>177±33</td>
<td>174±33</td>
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<tr>
<td>LDL cholesterol</td>
<td>110±29</td>
<td>108±29</td>
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<tr>
<td>Lipid-lowering medication (%)</td>
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<tr>
<td>Current cigarette smoker (%)</td>
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<td>22</td>
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<tr>
<td>Symptom Checklist-90-Revised Depression score‡‡</td>
<td>51±10</td>
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<tr>
<td>Verbal IQ§§</td>
<td>112±11</td>
<td>112±10</td>
</tr>
<tr>
<td>Full-scale IQ§§</td>
<td>114±10</td>
<td>114±10</td>
</tr>
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</table>

* Plus–minus values are means ±SD. ND denotes no data, and LDL low-density lipoprotein.
† Race was self-assigned. “White” denotes white, non-Hispanic.
‡ Adults are defined as persons 18 years of age or older.
§ P<0.01 by the Wilcoxon rank-sum test or the chi-square test comparing conventional and intensive treatment.
¶ The DCCT baseline value is the eligibility value.
‖ Visual acuity was measured with a Snellen chart. At baseline in the DCCT, all patients had visual acuity of 20/32 or better. In the EDIC study, visual acuity of 20/40 or worse in at least one eye was recorded in 44 patients.
** The DCCT baseline definition of peripheral neuropathy is pain or numbness in the hands only, taken from the Neurological History and Examination form. The EDIC study definition is pain or numbness in the hands or feet, taken from the Annual Medical History and Examination form.
†† To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
‡‡ Scores range from 30 to 80, with higher scores indicating worse performance.
§§ The normative mean IQ score is 100±15.
so that they had sufficient vision only to count fingers, and 20 patients (7 in the intensive-treatment group and 13 in the conventional-treatment group) had renal insufficiency.

During the entire 18-year follow-up, a total of 1355 episodes of coma or seizure were reported (896 in 262 patients in the intensive-treatment group and 459 in 191 patients in the conventional-treatment group) (Table 2). Of the 53 deaths during the DCCT and the EDIC study, 3 were attributed to hypoglycemia and all 3 occurred during the EDIC study.

Table 3 summarizes the raw scores for each test, stratified according to treatment group. The mean scores were well within normal limits when compared with those of a large sample of healthy persons without diabetes.25 Figure 1 shows the cognitive test results for each domain according to the original treatment assignment, the cumulative number of severe hypoglycemic events (zero, one to five, and more than five), and the degree of metabolic control (mean glycated hemoglobin values divided into thirds).

Neither the original treatment assignment nor the cumulative number of hypoglycemic events influenced performance in any cognitive domain. Higher values of glycated hemoglobin were associated with moderate declines in psychomotor efficiency (P<0.001) and motor speed (P=0.001). The degree of self-reported symptoms of depression, as indexed by median T scores from the Symptom Checklist-90-Revised, was also associated with poorer performance on measures of learning, immediate memory, and psychomotor efficiency. There were no significant interactions between any of the three key predictors (treatment-group assignment, frequency of severe hypoglycemic events, and glycated hemoglobin value) and any covariate.

The analyses were repeated using the broader definition of hypoglycemia, which includes episodes in which the patient is sufficiently incapacitated to require the assistance of another person. The results obtained with the use of the broad definition were similar to those obtained with the narrow definition.

The analyses were repeated again after exclusion of patients with a history of stroke, impaired vision, or severe kidney disease. The results were similar, with one exception: psychomotor efficiency was significantly worse (P=0.002) in patients receiving conventional therapy.

**Table 2. Severe Hypoglycemic Events.***

<table>
<thead>
<tr>
<th>No. of Events</th>
<th>DCCT</th>
<th>EDIC Study</th>
<th>Total 18-Yr Follow-up of the DCCT and the EDIC Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Events (no. of patients)</td>
<td>364</td>
<td>445</td>
<td>465</td>
</tr>
<tr>
<td>≥1 Event (no. of patients)</td>
<td>224</td>
<td>111</td>
<td>123</td>
</tr>
<tr>
<td>1–5 Events</td>
<td>190</td>
<td>104</td>
<td>119</td>
</tr>
<tr>
<td>&gt;5 Events†</td>
<td>34</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Total no. of events</td>
<td>653</td>
<td>205</td>
<td>243</td>
</tr>
</tbody>
</table>

* Severe hypoglycemic events were defined as those leading to coma or seizure. All hypoglycemic events from the DCCT are documented. Hypoglycemic events from the EDIC study are documented for the 3-month period before the annual visit.
† The number of events ranged from 6 to 23 in the intensive-treatment group and from 6 to 13 in the conventional-treatment group.

**DISCUSSION**

The increased risk of severe hypoglycemia, which accompanies intensive diabetes treatment aimed at achieving blood glucose levels in the normal range, remains one of the primary barriers to the implementation of such treatment. The potential cognitive consequences of severe hypoglycemia, including coma and seizure, are a key concern for clinicians, patients, and families. Patients often wonder whether recurrent hypoglycemia will lead to persistent problems in their ability to think or will have negative effects on school performance or future employability. Our study found no evidence of substantial long-term declines in cognitive function in a large group of patients with type 1 diabetes who were carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycemia.

These results do not mean that severe hypo-
Table 3. Raw Cognitive Test Scores.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Range of Scores†</th>
<th>At Entry into DCCT (1983–1989)</th>
<th>At Year 12 of EDIC Study (2005)</th>
<th>Normative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intensive Treatment (N=588)</td>
<td>Conventional Treatment (N=556)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intensive Treatment (N=588)</td>
<td>Conventional Treatment (N=556)</td>
<td></td>
</tr>
<tr>
<td>Problem solving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities (scaled scores)</td>
<td>1–19</td>
<td>12.6±2.5</td>
<td>12.7±2.4</td>
<td>14.0±2.2</td>
</tr>
<tr>
<td>Category test (no. of errors)</td>
<td>0–208‡</td>
<td>37.2±22.6</td>
<td>32.7±19.9</td>
<td>26.3±20.7</td>
</tr>
<tr>
<td>Learning (no. correct)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol-Digit Learning</td>
<td>0–28</td>
<td>24.1±4.5</td>
<td>24.3±4.4</td>
<td>24.1±4.5</td>
</tr>
<tr>
<td>Tactual Performance Memory</td>
<td>0–10</td>
<td>7.4±1.5</td>
<td>7.4±1.6</td>
<td>7.5±1.5</td>
</tr>
<tr>
<td>Immediate memory (no. correct)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Reproductions</td>
<td>0–17</td>
<td>14.7±2.1</td>
<td>14.6±2.3</td>
<td>14.3±2.4</td>
</tr>
<tr>
<td>Four-Word Short-Term Memory</td>
<td>0–60</td>
<td>40.3±9.1</td>
<td>39.6±9.6</td>
<td>39.0±10.5</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>0–43</td>
<td>20.0±5.8</td>
<td>19.6±5.5</td>
<td>20.0±6.9</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>0–9</td>
<td>7.7±1.6</td>
<td>7.8±1.5</td>
<td>7.5±1.8</td>
</tr>
<tr>
<td>Delayed recall (no. correct)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Reproductions</td>
<td>0–17</td>
<td>15.5±1.8</td>
<td>15.4±1.8</td>
<td>14.7±2.2</td>
</tr>
<tr>
<td>Logical Memory</td>
<td>0–43</td>
<td>16.4±5.5</td>
<td>16.2±5.4</td>
<td>17.1±6.3</td>
</tr>
<tr>
<td>Spatial information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embedded Figures (sec)</td>
<td>0–60‡</td>
<td>7.4±3.3</td>
<td>7.1±3.2</td>
<td>6.5±3.1</td>
</tr>
<tr>
<td>Object Assembly (scaled scores)</td>
<td>1–19</td>
<td>12.1±2.9</td>
<td>12.2±2.9</td>
<td>13.9±2.8</td>
</tr>
<tr>
<td>Block Design (scaled scores)</td>
<td>1–19</td>
<td>13.0±2.6</td>
<td>13.1±2.6</td>
<td>14.3±2.6</td>
</tr>
<tr>
<td>Tactual Performance Test (min)</td>
<td>0–30‡</td>
<td>10.9±3.8</td>
<td>10.8±3.8</td>
<td>11.4±4.8</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Vigilance (sec)‡</td>
<td>0–1000‡</td>
<td>368.3±72.5</td>
<td>378.3±86.4</td>
<td>388.1±88.5</td>
</tr>
<tr>
<td>Digit Vigilance (no. of errors)‡</td>
<td>0–100‡</td>
<td>4.5±5.1</td>
<td>4.8±5.3</td>
<td>7.7±8.3</td>
</tr>
<tr>
<td>Digit Span (scaled scores)</td>
<td>1–19</td>
<td>11.8±2.9</td>
<td>11.8±2.8</td>
<td>12.4±2.6</td>
</tr>
<tr>
<td>Psychomotor and mental efficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency (no. correct)</td>
<td>0–180</td>
<td>42.3±12.4</td>
<td>42.9±12.3</td>
<td>45.7±13.2</td>
</tr>
<tr>
<td>Digit Symbol, 90-sec total (no. correct)</td>
<td>10–90</td>
<td>65.1±11.1</td>
<td>65.0±11.0</td>
<td>62.3±11.4</td>
</tr>
<tr>
<td>Trail Making, part B (sec)</td>
<td>0–300‡</td>
<td>52.3±16.6</td>
<td>52.9±19.9</td>
<td>54.4±20.0</td>
</tr>
<tr>
<td>Grooved Pegboard, dominant hand (sec)</td>
<td>0–300‡</td>
<td>65.6±9.8</td>
<td>65.9±9.6</td>
<td>72.3±17.3</td>
</tr>
<tr>
<td>Grooved Pegboard, nondominant hand (sec)</td>
<td>0–300‡</td>
<td>70.2±12.3</td>
<td>70.0±11.0</td>
<td>79.0±18.6</td>
</tr>
<tr>
<td>Motor speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger Tapping, dominant hand (no. of taps in 10 sec)</td>
<td>0–80</td>
<td>48.7±6.5</td>
<td>48.7±7.0</td>
<td>50.6±7.3</td>
</tr>
<tr>
<td>Finger Tapping, nondominant hand (no. of taps in 10 sec)</td>
<td>0–80</td>
<td>44.6±6.0</td>
<td>44.7±6.1</td>
<td>45.3±6.7</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Normative data are based on approximately 175 adults without diabetes who were tested with the same test battery in the mid-to-late 1980s at the University of Pittsburgh Medical Center.
† Higher scores indicate better performance, except where noted.
‡ Higher scores indicate poorer performance.
§ P<0.01 by the Wilcoxon rank-sum test comparing conventional and intensive treatment.
glycemia is entirely benign. It is well established that an extended episode of profound hypoglycemia, such as one with a blood glucose level below 1.0 mmol per liter (18 mg per deciliter), can induce massive cerebral energy failure with a corresponding development of neuronal necrosis.\textsuperscript{26} Less severe episodes of severe hypoglycemia (e.g., those with a blood glucose level in the range of 2.8 to 3.6 mmol per liter [50 to 65 mg per deciliter]) are also known to disrupt brain activity transiently, can lead to short-term cognitive impairment, and can increase the risk of motor vehicle accidents.\textsuperscript{27,28} Nevertheless, with the exception of several small, cross-sectional studies,\textsuperscript{29-31} most researchers either have failed to find effects or have found only relatively weak effects of recurrent hypoglycemia on brain structure and function in children and adults with diabetes.\textsuperscript{6-8,32-35}

Previous examinations of the DCCT cohort found that after an average follow-up of 6.5 years, cognitive function was not adversely affected by recurrent severe hypoglycemia.\textsuperscript{5,10} In the EDIC study, after 18 years of follow-up of 85% of the available DCCT participants, no deleterious effects of previous intensive therapy or recurrent hypoglycemia were evident, despite the fact that our patients have had substantially longer exposure to diabetes and its glycemic changes, have had more episodes of severe hypoglycemia, and are now entering a later phase of their lives. By using the same comprehensive, extensively validated test battery that has been used in many other studies, we can draw conclusions about the longitudinal course of cognitive functioning in patients with type 1 diabetes. Our findings of minimal or no effects of either previous intensive treatment or severe hypoglycemia should be reassuring for patients with type 1 diabetes for whom intensive therapy is strongly recommended.

Better glycemic control may have subtle beneficial effects on cognitive ability, mirroring the recognized benefit of near-normal glycemic control to the retina, kidney, peripheral nerves, and cardiovascular system.\textsuperscript{34-37} For example, those patients with worse metabolic control (glycated hemoglobin values \( \geq 8.8\% \)) performed approximately 9% more slowly on measures of psychomotor efficiency than those with better control (glycated hemoglobin \( <7.4\% \)). Our findings are consistent with recent literature demonstrating that poor metabolic control, with subsequent development

![Figure 1. Effects of DCCT Treatment Group, Severe Hypoglycemia, and Glycated Hemoglobin on Changes in Cognition, from Entry into DCCT to Year 12 in the EDIC Study.](image-url)

The bars show the changes within cognitive domains between cognitive testing at baseline in DCCT and follow-up testing (a mean of 18 years after baseline) expressed as changes in z scores for intensive versus conventional treatment (Panel A), frequency of episodes of severe hypoglycemia (coma or seizure) (Panel B), and mean glycated hemoglobin values (Panel C). Across the three groups, higher levels of glycated hemoglobin were associated with moderate declines in psychomotor efficiency (\( P=0.001 \)) and motor speed (\( P=0.001 \)), but no other cognitive domain was affected significantly. Cognitive domains are numbered as follows: 1, problem solving; 2, learning; 3, immediate memory; 4, delayed recall; 5, spatial information; 6, attention; 7, psychomotor efficiency; and 8, motor speed.
of micro- and macrovascular complications, is associated with the development of mild cognitive impairments\textsuperscript{35,36} and subtle abnormalities in brain structure\textsuperscript{37} and activation.\textsuperscript{38} These structural and functional changes, which may reflect cerebral microangiopathy,\textsuperscript{39,40} are moderate in degree. Moreover, there is no evidence that they adversely affect patients’ activities of daily living. Efforts to prevent the occurrence of microvascular complications may reduce the risk of neurocognitive deficits as well. The relationship noted between higher levels of depressive symptoms and poorer performance on measures of learning and memory is consistent with the extensive literature indicating that depression can adversely affect cognitive function, independent of other biomedical and psychosocial characteristics.\textsuperscript{41}

The long-term, comprehensive follow-up study presented here has substantial strengths; however, there are notable gaps that must be kept in mind. Although some patients received a diagnosis of diabetes as very young children, this subgroup is small, and systematic data on glycated hemoglobin values and severe hypoglycemic events before they entered the DCCT are not available. We also do not have information about the effects of intensive therapy on the elderly or those living for more than 30 years with diabetes. Finally, these results from the selected DCCT cohort should be applied carefully to the total population of patients with type 1 diabetes.

The findings of this study provide an important message about the safety of intensive diabetes therapy for those receiving a diagnosis of diabetes as adolescents or young adults. Within the aforementioned limits, we can be confident that although acute hypoglycemic events can be dangerous at the time they occur, recurrent severe episodes associated with intensive diabetes therapy, as administered in the DCCT, do not appear to have long-term adverse effects on the cognitive capacity of patients with type 1 diabetes. This conclusion lends further support to the use of intensive diabetes therapy to reduce the long-term risks of retinopathic, nephropathic, neuropathic, and cardiovascular complications in type 1 diabetes.

Supported by a grant (5 R01 DK062218-02) from and contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and by the General Clinical Research Centers Program, National Center for Research Resources.

Dr. Jacobson reports serving on medical advisory boards for Pfizer and Amylin. Dr. Ryan reports receiving consulting fees from GlaxoSmithKline and Amylin and lecture fees from Eli Lilly. No other potential conflict of interest relevant to this article was reported.

APPENDIX


30. Gold AE, Deary IJ, Jones RW, O’Hare JP, Reckless JPD, Frier BM. Severe deterioration in cognitive function and personality in five patients with long-standing di-
Use of Physicians’ Services under Medicare’s Resource-Based Payments

Stephanie Maxwell, Ph.D., Stephen Zuckerman, Ph.D., and Robert A. Berenson, M.D.

BACKGROUND
In 1992, Medicare implemented the resource-based relative-value scale, which established payments for physicians' services based on relative costs. We conducted a study to determine how the use of physicians' services changed during the first decade after the implementation of this scale.

METHODS
With the resource-based relative-value scale, Medicare payments are based on the number of relative-value units (RVUs) assigned to physicians' services. The total number of RVUs reflects the volume of physicians' work (the time, skill, and training required for a physician to provide the service), practice expenses, and professional-liability insurance. Using national data from Medicare on physicians' services and American Medical Association files on RVUs, we analyzed the growth in RVUs per Medicare beneficiary from 1992 to 2002 according to the type of service and specialty. We also examined this growth with respect to the quantity and mix of services, revisions in the valuation of RVUs, and new service codes.

RESULTS
Between 1992 and 2002, the volume of physicians' work per Medicare beneficiary grew by 50%, and the total RVUs per Medicare beneficiary grew by 45%. The quantity and mix of services were the largest sources of growth, increasing by 19% for RVUs for physicians' work and by 22% for total RVUs. Our findings varied among services and specialties. Revised valuation of RVUs was a key source of the growth in RVUs for physicians' work and total RVUs for evaluation and management and for tests. New service codes were the largest drivers of growth for major procedures (accounting for 36% of the growth in RVUs for physicians' work and 35% of the growth in total RVUs), and the quantity and mix of existing services were the largest drivers of growth for imaging. The growth in RVUs for physicians' work was greatest in cardiology (114%) and gastroenterology (72%). The total growth in RVUs was greatest in cardiology (99%) and dermatology (105%).

CONCLUSIONS
In the first 10 years after the implementation of the resource-based relative-value scale, RVUs per Medicare beneficiary grew substantially. The leading sources of growth varied among service types and specialties. An understanding of these sources of growth can inform policies to control Medicare spending.
In 1992, Medicare implemented the resource-based relative-value scale, which established payments for physicians’ services based on relative costs instead of prevailing charges. The goal of the new system was to correct distortions caused by charge-based payments and to encourage efficiencies in medical practice.¹ With the use of this scale, payments are based on the number of relative-value units (RVUs) assigned to each service. Total RVUs for a given service reflect three cost components: physicians’ work (the time, skill, and training required for a physician to provide the service), practice expenses, and professional-liability insurance. The costs associated with each component are assigned a weight, or index value, and are adjusted to account for differences in practice expenses in different geographic locations. The three index values for a service are then summed and multiplied by a standard dollar amount (a “conversion factor”) to arrive at a payment amount. On average, physicians’ work accounts for 52% of total payments to physicians, practice expenses account for 44%, and professional-liability insurance accounts for 4%.² Overall, Medicare payments represent approximately 20% of the revenues that physicians receive, although the share varies according to the physician’s specialty.³

Early policy simulations suggested that when the resource-based relative-value scale was phased in (by 1995), it would increase payments for evaluation and management services by 25 to 30%, decrease payments for procedures by 25%,⁴ and redistribute overall payments toward evaluation and management services⁵ and the physicians’ specialties that furnish mainly those services.⁶ Medicare’s relative values for practice expenses and professional-liability insurance were based on historical charges until 1999 and 2000, respectively, when resource-based values for these components were phased in. By 2002, the entire system’s relative values were derived from estimates of resource costs. Like the original resource-based relative-value scale, the shift to resource-based values for practice expenses and professional-liability insurance was intended to better align payments with resource costs, and this shift was expected to redistribute payments toward evaluation-oriented services.

The resource-based relative-value scale was never expected to control overall Medicare spending on physicians. To do that, Congress established performance standards based on the volume of physicians’ services and, in 1997, a sustainable growth rate for use in determining the annual update to the conversion factor.⁶,⁷ Recently, Congress has overridden these policies and determined the updates without strictly adhering to the sustainable growth rate, because this rate would have resulted in annual reductions in Medicare fees.

The Centers for Medicare and Medicaid Services (CMS) maintains the resource-based relative-value scale, relying on recommendations from the Specialty Society Relative Value Update Committee of the American Medical Association (AMA). During the first 10 years after its introduction, the scale was altered annually to introduce new service codes and make revisions to codes for which definitions had been modified. In addition, two comprehensive reviews (known as 5-year reviews) of relative values for physicians’ work were performed in 1997 and 2002, as required by statute.⁸,⁹ Policymakers and stakeholders focus on these refinements to the scale and on the annual update, since they are the main policy levers that influence Medicare spending on physicians’ services. However, other factors play important roles in determining the growth and distribution of Medicare’s spending on physicians. Most directly, growth in the number of beneficiaries adds to spending, even if the fee schedule remains static. Spending also increases as a result of the introduction and application of new service codes and the expanded application of existing services.

The literature on Medicare’s resource-based relative-value scale includes assessments of the early effects of the system on all specialties⁴,⁶ and numerous articles on its effects on particular specialties.¹⁰,¹¹ However, we are not aware of recent or cumulative assessments of the effect of the scale on all service types or major specialties or of examinations of the sources of changes to the scale. We analyzed the overall growth in the volume of physicians’ services per Medicare beneficiary during the first 10 years after the introduction of the Medicare fee schedule. We also examined the contributions to that growth that were made by refinements of existing service codes in the scale, the addition of new codes, and the growth in the quantity and mix of existing services.

METHODS

DATA
We used annual claims files from the CMS for data on the use of Medicare physicians’ services in 1992 and 2002. We obtained files on RVUs for 1992...
through 2002 from the AMA. Files on RVUs list the values for physicians’ work, practice expenses, and professional-liability insurance for each service paid for through the Medicare fee schedule. Using these files and claims files from 1992 and 2002, we calculated the RVUs for physicians’ work and total RVUs for services paid for through the Medicare fee schedule in those years. We also obtained a file from the AMA that identified the review status of all services ever paid for through the Medicare fee schedule. Categories for the review status included new codes, codes reviewed during the first or second 5-year review, codes reviewed during the annual review process, and codes not yet reviewed.

**CALCULATIONS OF SERVICE VOLUME**

An RVU is the unit of measure for the resource-based relative-value scale; each service is assigned a specific number of RVUs according to its relative resource costs. Since payment rates are determined by multiplying RVUs by a single conversion factor, RVUs are analogous to relative payment rates. In this study, we used RVUs to calculate an intensity-weighted measure of the quantity of service — this measure is called “RVU volume.” Thus, RVU volume in a given year is the sum, for all services, of the number of units of each service multiplied by the RVU value assigned to that service in that year. We calculated the RVU volume for physicians’ work and total RVUs (which includes RVUs for physicians’ work, practice expenses, and professional-liability insurance). We accounted for the increase in Medicare beneficiaries over the 10-year period by dividing the RVU volume for physicians’ work and total RVU volume in 2002 by the number of beneficiaries in 2002 and the RVU volume amounts in 1992 by the number of beneficiaries in 1992.

We calculated the aggregate percent change in the RVU volume for physicians’ work and the total RVU volume per beneficiary over the 10-year period, for all services and according to service type and specialty, as follows: \[ \left( \frac{\text{RVU volume in 2002} - \text{RVU volume in 1992}}{\text{RVU volume in 1992}} \right) \times 100. \] We also examined changes in the percent distribution of the RVU volume for physicians’ work and total RVU volume per beneficiary among service types and specialties.

We then calculated three components of the aggregate change in the RVU volume of physicians’ work and the total RVU volume per beneficiary: changes in the quantity and mix of services from 1992 through 2002, revisions of the valuation of RVUs for existing services, and the introduction of new service codes after 1992. We used the following calculation for changes in the quantity and mix of services: \[ \left( \frac{\text{the quantity of existing services in 2002} \times \text{1992 RVU values for each service}}{\text{the quantity of existing services in 1992} \times \text{1992 RVU values}} - 1 \right) \times 100. \] Policymakers and researchers use such a calculation of the quantity and mix of services when analyzing changes in the volume of physicians’ services.

We calculated revisions of the valuation of RVUs as follows: \[ \left( \frac{\text{the quantity of existing services in 2002} \times \text{2002 RVU values for each service}}{\text{the quantity of existing services in 2002} \times \text{1992 RVU values}} - 1 \right) \times 100. \] This calculation reflects the effect of “price” changes for existing services due to RVU revisions made by the CMS and the Relative Value Update Committee of the AMA.

We used the following calculation for the introduction of new service codes: \[ \left( \frac{\text{the quantity of all existing and new services in 2002} \times \text{2002 RVU values for each service}}{\text{the quantity of existing services in 2002} \times \text{2002 RVU values}} - 1 \right) \times 100. \] This calculation reflects the effect of new service codes.

These three component rates of growth, when multiplied together, are equal to the aggregate growth rate calculated above. To present our results in a clinically meaningful way, we analyzed physicians’ services, using the Berenson–Eggers Type of Service system, which classifies services into 104 service groups. We present data for five summary service groups in this system: evaluation and management, imaging, major procedures, other procedures, and tests. Major procedures include coronary-artery bypass grafting and hip and knee replacements; other procedures include cataract extraction, colonoscopy and other endoscopic procedures, and routine dermatologic procedures. We identified the top 10 specialties in terms of their share of Medicare spending for physicians’ services in 2002. These 10 specialties accounted for more than 70% of Medicare spending for physicians: internal medicine, family practice, cardiology, ophthalmology, diagnostic radiology, orthopedics, general surgery, dermatology, urology, and gastroenterology.

For our analyses, we assigned each service code to one of four hierarchical groups according to the review status: new codes (i.e., codes present in 2002 claims but not in 1992 claims), codes in one or both 5-year reviews, codes in annual reviews, and codes not yet reviewed. New codes represent...
both new services and services replacing previous procedures or techniques. Without this hierarchy, 10% of the codes would fall into multiple groups.

**RESULTS**

During the first decade that the resource-based relative-value scale was used, the overall RVU volume per beneficiary for physicians’ work grew by 50% (Table 1). The RVU volume per beneficiary grew more slowly for evaluation and management services (39.5%) but grew more rapidly for imaging (62.5%), other procedures (68.2%), and tests (184.8%, from a very small value in 1992). The share of the RVU volume that was accounted for by evaluation and management services decreased by 4.2 percentage points over the decade, whereas the shares for imaging, other procedures, and tests increased (Table 1).

Of the three components that affected growth, the quantity and mix of services accounted for the most growth in the overall RVU volume for physicians’ work (18.8%). Revisions in the valuation of RVUs accounted for 14.8% of overall growth, and new service codes accounted for 10.0%. These percentages for all three components, when multiplied together according to our method, equal the percentage of overall growth. For example, \((1 + 0.188) \times (1 + 0.148) \times (1 + 0.100) - 1 \times 100\) is equal to the 50% growth in the RVUs for physicians’ work.

The relative importance of these components varied among the three service types. Growth in the volume of RVUs per beneficiary for imaging work was due mainly to the growth in the quantity and mix of services (38.4%). Growth in the RVUs for major procedures was due mainly to new service codes (35.6%). Finally, growth in the RVUs for tests was due mainly to revisions in the valuations of the RVUs (68.2%).

In general, growth in the volume of total RVUs was similar to growth in the volume of RVUs for physicians’ work, but there was less variation among service types (Table 1). The differences between growth in the volume of RVUs for physicians’ work and total RVUs were due mainly to

<table>
<thead>
<tr>
<th>RVU Component and Service Category†</th>
<th>Distribution of RVUs</th>
<th>Mean RVUs per Medicare Beneficiary</th>
<th>10-Year Change in RVUs per Medicare Beneficiary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1992</td>
<td>2002</td>
<td>1992</td>
</tr>
<tr>
<td>Physicians’ work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>100.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Evaluation and management</td>
<td>59.9</td>
<td>55.7</td>
<td>9.4</td>
</tr>
<tr>
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<td>8.4</td>
<td>9.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Major procedures</td>
<td>11.5</td>
<td>11.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Other procedures</td>
<td>18.9</td>
<td>21.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Tests</td>
<td>1.3</td>
<td>2.5</td>
<td>0.2</td>
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<tr>
<td>Physicians’ work, practice expenses, and liability insurance</td>
<td></td>
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<td></td>
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<tr>
<td>Overall</td>
<td>100.0</td>
<td>100.0</td>
<td>31.0</td>
</tr>
<tr>
<td>Evaluation and management</td>
<td>49.5</td>
<td>49.5</td>
<td>15.4</td>
</tr>
<tr>
<td>Imaging</td>
<td>11.8</td>
<td>14.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Major procedures</td>
<td>13.1</td>
<td>10.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Other procedures</td>
<td>22.6</td>
<td>22.6</td>
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</tr>
<tr>
<td>Tests</td>
<td>3.0</td>
<td>3.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Data are from physicians’ Medicare claims and files on RVUs from 1992 to 2002. Percentages may not sum to 100 because of rounding. There were 33,956,000 Medicare beneficiaries in 1992 and 38,088,000 Medicare beneficiaries in 2002.14
† Service categories are based on the Berenson–Eggers Type of Service classification.
the introduction of resource-based RVUs for practice expenses and professional-liability insurance. This change lowered the total RVUs for many services, which offset some of the growth in the volume of RVUs for physicians' work. Consequently, the growth in the total RVU volume due to revisions in the valuation of RVUs was only 7.6%. The revisions in the valuation of RVUs for practice expenses and professional-liability insurance resulted in a decrease in the total RVU volume for imaging (−6.9%), major procedures (−14.7%), and other procedures (−1.1%).

Changes in the RVU volume for physicians' work and the total volume per beneficiary varied among the top 10 specialties (Table 2). Cardiology had the largest overall growth in the RVU volume for physicians' work (113.6%), whereas urology had a decrease in the RVU volume (−1.0%). Three specialties in particular exhibited substantial growth in the RVU volume for physicians' work due to the quantity and mix of services: cardiology (52.0%), dermatology (41.4%), and gastroenterology (49.4%). Revisions in the valuation of RVUs were the leading sources of growth in the RVU volume for physicians' work in internal medicine (20.1%) and general surgery (23.8%).

For all specialties, growth in the total RVU volume and the three components of that growth (Table 2) differed from growth of the RVU volume for physicians' work mainly because of the intro-

<table>
<thead>
<tr>
<th>RVU Component and Specialty</th>
<th>Distribution of RVUs</th>
<th>10-Year Change in RVUs per Medicare Beneficiary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1992</td>
<td>2002</td>
</tr>
<tr>
<td>Physicians' work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>17.6</td>
<td>15.8</td>
</tr>
<tr>
<td>Cardiology</td>
<td>6.6</td>
<td>9.7</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>10.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Diagnostic radiology</td>
<td>7.7</td>
<td>7.3</td>
</tr>
<tr>
<td>Family practice</td>
<td>8.4</td>
<td>7.6</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>4.6</td>
<td>4.9</td>
</tr>
<tr>
<td>General surgery</td>
<td>6.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Dermatology</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Urology</td>
<td>3.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>2.9</td>
<td>3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physicians' work, practice expenses, and liability insurance</th>
<th>Distribution of RVUs</th>
<th>10-Year Change in RVUs per Medicare Beneficiary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1992</td>
<td>2002</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>16.0</td>
<td>14.6</td>
</tr>
<tr>
<td>Cardiology</td>
<td>7.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>12.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Diagnostic radiology</td>
<td>8.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Family practice</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>General surgery</td>
<td>6.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Dermatology</td>
<td>2.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Urology</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>3.1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* Data are from physicians' Medicare claims and files on RVUs from 1992 to 2002. There were 33,956,000 Medicare beneficiaries in 1992 and 38,088,000 Medicare beneficiaries in 2002.14
duction of resource-based RVUs for practice expenses and professional-liability insurance. The growth of total RVUs due to revisions in their valuations differed substantially from the growth of RVUs for physicians’ work in all specialties except internal medicine.

To further understand the sources of growth in the RVU volume for physicians’ work, we examined the distribution of service codes and the RVU volume for physicians’ work according to the review activity of the CMS and the Relative Value Update Committee (Fig. 1). The service codes examined during these comprehensive reviews accounted for only 23% of all the codes, but they accounted for 66% of the RVU volume of physicians’ work. Given the influence of the comprehensive reviews, we examined them closely. During the first 5-year review, values for physicians’ work were increased for only 30.6% of the service codes, but these codes accounted for 82.0% of the RVU volume for physicians’ work under review (Table 3). During the second 5-year review, the values of RVUs increased for a large share of codes (55.7%), but this increase accounted for a smaller share of the RVU volume for physicians’ work under review (38.0%). In both 5-year reviews, relatively few codes were reduced in value (10.9% during the first review and 3.6% during the second review).

Table 4 provides examples of service codes in three categories of volume growth: codes for which there were substantial increases in the frequency of use, those that were revised to higher values, and those introduced after 1992. The first category includes a range of services that were used more frequently after 1992 and were used very frequently in 2002. The second category includes some codes in which the valuation of either the RVU for physicians’ work or the total RVU per service increased substantially. The third category includes new codes. Some have particularly high RVU values; others are used frequently. The services listed in Table 4 are examples of service types within each of these three categories. There may have been larger increases or even decreases in the use or valuation of RVUs for other services.

**Discussion**

Our findings show that the volume of physicians’ services per Medicare beneficiary grew considerably during the first decade after the resource-based relative-value scale was introduced. This growth varied among services and specialties and resulted in a redistribution of the total RVU volume per beneficiary (a close counterpart to Medicare spending on physicians). We examined the role of three key factors affecting growth in the RVU volume per beneficiary: increases in the quantity and mix of services, revisions of the valuation of RVUs for existing codes, and the introduction of new codes. In terms of the total RVU volume per beneficiary, the volume of imaging services increased the most because of a dramatic increase in the quantity and mix of services. Among all services, the volume of major procedures increased the least, with the introduction of new codes (both to represent new services and to replace previous procedures) accounting for most...
of the growth. Because of these growth patterns, imaging services gained a greater share of the distribution of total RVU volume. The share of total RVU volume accounted for by evaluation and management services remained the same because of increases in the valuation of RVUs for physicians’ work in these services and introduction of resource-based RVUs for practice expenses and professional-liability insurance, which offset the declining relative volume.

In terms of work volume, values for the majority of services (84%) in 2002 reflect a combination of new, reviewed, and revised service codes, rather than the values from the original resource-based relative-value scale. The share of volume affected by these changes in service codes increased in January 2007, when CMS implemented changes based on its third 5-year review of RVUs for physicians’ work. That review, which was conducted in 2006, focused on high-frequency service codes that had not been reviewed before and on another review of codes for evaluation and management.²² The Medicare Payment Advisory Commission recently described weaknesses in the 5-year review process for valuing physicians’ work and proposed improvements to the process for addressing potentially overvalued codes.²³,²⁴ A major concern was the lack of a mechanism for identifying and correcting overvalued services. The commission’s view was that the RVUs for physicians’ work in providing any service should be reduced if the level of work effort needed to furnish the service declines as physicians gain experience with the service.

We did not explicitly examine the relationship between changes in the supply of physicians and the services provided. However, we analyzed external data on changes in the number of physicians and concluded that the relative growth in the number of physicians among the 10 specialties in this analysis does not track directly with the growth in the total RVU volume or RVUs for physicians’ work.²⁵-²⁷ For example, the three specialties with the greatest increases in the numbers of physicians — family practice, gastroenterology, and internal medicine — are not the three specialties with the greatest growth in the volume of RVUs for physicians’ work and the total RVU volume — dermatology, cardiology, and orthopedics.

A potential limitation of our study is that it measured what occurred during the first 10 years of the fee schedule and does not reflect more recent data and policy developments. However, we think that current policy developments and trends reinforce our findings. For example, although the CMS recently announced that the RVUs for physicians’ work associated with certain higher-level evaluation and management codes increased by 29 to 37% (as a result of the third 5-year review), the overall effect of these changes on evaluation and management services was significantly smaller for two reasons.²⁸ First, many other values for evaluation and management services were not increased under the third 5-year review, and second, the CMS reduced all RVUs for physicians’ work by 10% as a budget-neutrality adjustment. Furthermore, RVUs for physicians’ work account for only about half of the total RVUs. These factors dilute the effect of the increases in evaluation and management services, and the CMS estimated that this year, internists and family physicians, for example, will each receive only a 5% increase in payments as a result of the increases from the third 5-year review.²⁹

Furthermore, our findings suggest that new service codes have a strong influence on the growth and distribution of RVUs for physicians’ work.

### Table 3. Distribution of Services and RVUs for Physicians’ Work According to Valuation Changes.²⁶

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Service Codes (N = 932)</td>
<td>Distribution of RVUs</td>
</tr>
<tr>
<td></td>
<td>no. (%) &amp; (%)</td>
<td>%</td>
</tr>
<tr>
<td>Increased</td>
<td>285 (30.6) &amp; 82.0</td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td>102 (10.9) &amp; 2.4</td>
<td></td>
</tr>
<tr>
<td>Remained the same</td>
<td>545 (58.5) &amp; 15.7</td>
<td></td>
</tr>
</tbody>
</table>

* Data are from Medicare physicians’ claims and files on RVUs from 1992 to 2002.
work and total RVU volume. This influence may be increasing, since new codes continue to be introduced. Since 2002, approximately 800 codes have been added to the Medicare fee schedule, and about 275 existing codes have been deleted; the total number of codes for which RVUs are determined now approaches 7000.\(^{30}\) Finally, our findings show that the RVU volume has grown at different rates among service types. The overall patterns we identified have continued. Most recently, imaging has been the fastest-growing service type, followed by other procedures and tests, whereas the volume of evaluation and management services and the volume of major procedures have grown much more slowly.\(^{31}\)

Recent trends and policy decisions overall are consistent with our findings and reinforce the importance of understanding the roles of new service codes, revised valuation of RVUs, and the quantity and mix of services in the growth and distribution of the volume of physicians' services and, by extension, payments. Furthermore, as long as the sustainable growth rate that controls the aggregate growth in spending remains in place, Medicare payment to physicians is essentially a zero-sum game. Thus, differences in rates of

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**Table 4. Examples of Service Codes Contributing to the Growth in RVUs between 1992 and 2002.\(^*\)**

<table>
<thead>
<tr>
<th>Type of Code</th>
<th>CPT Code</th>
<th>CPT Description</th>
<th>RVUs for Physicians' Work</th>
<th>Frequency of Service (per 100,000 Medicare Beneficiaries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billed more frequently in 2002 than in 1992</td>
<td>99214</td>
<td>Office or outpatient visit, established patient, 25-min visit</td>
<td>0.93 1.10</td>
<td>76,964 116,564</td>
</tr>
<tr>
<td></td>
<td>88305</td>
<td>Tissue examination by pathologist</td>
<td>0.79 0.75</td>
<td>22,201 39,064</td>
</tr>
<tr>
<td></td>
<td>93320</td>
<td>Doppler echocardiographic examination of heart</td>
<td>0.39 0.38</td>
<td>7,750 16,563</td>
</tr>
<tr>
<td></td>
<td>99285</td>
<td>Emergency department visit</td>
<td>2.79 3.06</td>
<td>6,020 14,102</td>
</tr>
<tr>
<td></td>
<td>99243</td>
<td>Office consultation</td>
<td>1.56 1.72</td>
<td>5,076 11,671</td>
</tr>
<tr>
<td></td>
<td>70450</td>
<td>Computed tomographic scan of head or brain without dye</td>
<td>0.90 0.85</td>
<td>5,051 9,841</td>
</tr>
<tr>
<td>Revised to higher values in 2002 than in 1992</td>
<td>17304</td>
<td>Micrographic surgery to remove malignant skin lesion, up to 5 tissue specimens examined</td>
<td>5.84 7.60</td>
<td>228 757</td>
</tr>
<tr>
<td></td>
<td>99244</td>
<td>Office consultation</td>
<td>2.29 2.58</td>
<td>6,858 12,475</td>
</tr>
<tr>
<td></td>
<td>99213</td>
<td>Office or outpatient visit, established patient, 15-min visit</td>
<td>0.58 0.67</td>
<td>226,374 280,009</td>
</tr>
<tr>
<td></td>
<td>67210</td>
<td>Treatment of retinal lesion</td>
<td>6.75 8.82</td>
<td>391 514</td>
</tr>
<tr>
<td></td>
<td>43832</td>
<td>Placement of gastrostomy tube</td>
<td>11.25 15.60</td>
<td>38 7</td>
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<tr>
<td></td>
<td>44140</td>
<td>Partial removal of colon</td>
<td>15.39 21.00</td>
<td>318 207</td>
</tr>
<tr>
<td></td>
<td>44950</td>
<td>Appendectomy</td>
<td>6.39 10.00</td>
<td>36 29</td>
</tr>
<tr>
<td></td>
<td>47120</td>
<td>Partial removal of liver</td>
<td>25.12 35.50</td>
<td>6 6</td>
</tr>
<tr>
<td>New</td>
<td>33533</td>
<td>Coronary-artery bypass grafting with the use of a single arterial graft</td>
<td>NA 30.00</td>
<td>NA 577</td>
</tr>
<tr>
<td></td>
<td>27245</td>
<td>Treatment of thigh fracture</td>
<td>NA 20.31</td>
<td>NA 66</td>
</tr>
<tr>
<td></td>
<td>53850</td>
<td>Prostatic microwave thermotherapy</td>
<td>NA 9.45</td>
<td>NA 47</td>
</tr>
<tr>
<td></td>
<td>66172</td>
<td>Incision of eye</td>
<td>NA 15.04</td>
<td>NA 32</td>
</tr>
<tr>
<td></td>
<td>33863</td>
<td>Placement of ascending aortic graft</td>
<td>NA 45.00</td>
<td>NA 8</td>
</tr>
<tr>
<td></td>
<td>92135</td>
<td>Diagnostic imaging of eye</td>
<td>NA 0.35</td>
<td>NA 4202</td>
</tr>
<tr>
<td></td>
<td>92980</td>
<td>Insertion of intracoronary stent</td>
<td>NA 14.84</td>
<td>NA 859</td>
</tr>
</tbody>
</table>

\(^*\) Data are from physicians' Medicare claims and files on RVUs from 1992 to 2002. CPT denotes current procedural terminology, and NA not available.
growth in the RVU volume of physicians’ work and the total RVU volume among service types and specialties affect the overall costs to Medicare, and they should be considered in policies to control Medicare spending.

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

The opinions expressed herein are those of the authors and do not necessarily reflect those of the Medicare Payment Advisory Commission or the Urban Institute, its trustees, or its sponsors.

REFERENCES

29. Centers for Medicare and Medicaid Services. Medicare program: five-year review of work relative value units under the physician fee schedule and proposed changes to the practice expense methodology; notice. Fed Regist 2006;71(125):37255.
Superior Vena Cava Syndrome with Malignant Causes

Lynn D. Wilson, M.D., M.P.H., Frank C. Detterbeck, M.D., and Joachim Yahalom, M.D.


A 58-year-old man presents with a 2-week history of progressive dyspnea on exertion, neck swelling, decreased appetite, and fatigue. There is no history of syncope or dysphagia. He smoked cigarettes until 5 years ago. The physical examination reveals a heart rate of 105 beats per minute, a respiratory rate of 20 breaths per minute, and superficial vascular distention over the neck, chest, and upper abdomen. Stridor is not present. How should his case be evaluated and managed?

The Clinical Problem

The superior vena cava syndrome, which occurs in approximately 15,000 persons in the United States each year, encompasses a constellation of symptoms and signs resulting from obstruction of the superior vena cava. The increased venous pressure in the upper body results in edema of the head, neck, and arms, often with cyanosis, plethora, and distended subcutaneous vessels (Fig. 1A). Edema may cause functional compromise of the larynx or pharynx, manifested as cough, hoarseness, dyspnea, stridor, and dysphagia. Cerebral edema may lead to headache, confusion, and coma. The decreased venous return may result in hemodynamic compromise; this complication may be a consequence of obstruction of the superior vena cava (intrinsic or due to extrinsic compression), compression of the heart by a large mass in the chest, or both. Symptoms develop over a period of 2 weeks in approximately a third of patients, and over longer periods in other cases.1-5

Anatomy and Physiology

The superior vena cava carries blood from the head, arms, and upper torso to the heart; it carries approximately one third of the venous return to the heart. Compression of the superior vena cava may result from the presence of a mass in the middle or anterior mediastinum (generally to the right of midline), consisting of enlarged right paratracheal lymph nodes, lymphoma, thymoma, an inflammatory process, or an aortic aneurysm, for example. Thrombosis of the superior vena cava without extrinsic compression can also occur (Fig. 1B).

When the superior vena cava is obstructed, blood flows through a collateral vascular network to the lower body and the inferior vena cava or the azygos vein. It generally takes several weeks for the venous collaterals to dilate sufficiently to accommodate the blood flow of the superior vena cava.6,7 In humans with obstruction of the superior vena cava, the cervical venous pressure is usually increased to 20 to 40 mm Hg (normal range, 2 to 8 mm Hg).8-10 The severity of the symptoms depends on the degree of narrowing of the superior vena cava and the speed of the onset of the narrowing.
Edema in the upper body as a result of obstruction of the superior vena cava is visually striking but often of little consequence. However, cerebral edema, although rare, can be serious or fatal. The upper respiratory tract may become narrowed by nasal and laryngeal edema. Serious effects of obstruction of the superior vena cava are rare; among 1986 patients with obstruction of the superior vena cava, only one death was documented. In case reports of neurologic or laryngeal compromise, it is unclear whether other contributing factors such as brain metastases or tracheal compression were present.

**Figure 1. The Superior Vena Cava Syndrome.**

Clinical findings in a patient with the superior vena cava syndrome, including facial edema, plethora, jugular venous distention, and prominent superficial vascularity of neck and upper chest, are shown in Panel A. The vascular anatomy of the upper chest, including the heart, superior vena cava, inferior vena cava, and subclavian vessels, is shown in Panel B. The tumor is shown compressing the superior vena cava.

**Etiologic Factors**

Infectious causes (especially syphilitic aortic aneurysm and tuberculosis) accounted for the majority of cases of obstruction of the superior vena cava until about 50 years ago. These causes became rare, and malignant conditions accounted for more than 90% of cases approximately 25 years ago. Currently, obstruction of the superior vena cava caused by thrombosis or nonmalignant conditions accounts for approximately 35% of cases, reflecting the increased use of intravascular devices such as catheters and pacemakers. The most common malignant causes are non–small-cell lung cancer...
(approximately 50% of patients), small-cell lung cancer (approximately 25% of patients), lymphoma, and metastatic lesions (each approximately 10% of patients); the clinical features that may suggest these diagnoses are summarized in Table 1.1,4,5,13,15,17

Recognition of a nonmalignant cause of the superior vena cava syndrome is typically straightforward, particularly when the syndrome is associated with the use of an implanted intravascular device. An aortic aneurysm is easily recognized on computed tomography (CT). The diagnosis of fibrosing mediastinitis, although a rare cause, requires a biopsy.

**STRATEGIES AND EVIDENCE**

**CLINICAL EVALUATION**

Clinical diagnosis of obstruction of the superior vena cava is made on the basis of signs and symptoms (Table 2).1,4,5,13,15,18 The history taking should attend to the duration of symptoms, previous diagnoses of malignant conditions, or previous intravascular procedures. In most cases, symptoms are progressive over several weeks, and in some cases they may improve as collateral circulation develops. The severity of the symptoms is important in determining the urgency of intervention.

**Imaging**

The most useful imaging study is CT of the chest after the administration of contrast material (which is needed to evaluate the superior vena cava). Complications, including excessive bleeding from the venipuncture sites and reactions to contrast medium, are uncommon.11,14,19 Venography is generally warranted only when an intervention (placement of a stent or surgery) is planned.20 Magnetic resonance imaging may be useful for patients who cannot tolerate the contrast medium. Positron-emission tomography (PET) is sometimes useful, because it may influence the design of the radiotherapy field (Fig. 2).21

The clinical history combined with CT imaging will generally differentiate between vena caval thrombosis and extrinsic compression. A tissue diagnosis is necessary to confirm the presence of malignant conditions. Clinical assessment is warranted to determine whether a peripheral biopsy site (e.g., a palpable supraclavicular lymph node) might be accessible before proceeding to an invasive procedure such as mediastinoscopy for tissue diagnosis. Cytologic examination of the sputum may result in diagnosis in patients who have endobronchial cancer. Pleural effusion is common (affecting about two thirds of patients with the superior vena cava syndrome); thoracentesis and cytologic analysis should be strongly considered because they are simple to perform and expedient, although they yield a diagnosis in only about 50% of such patients.15 Bronchoscopy has a diagnostic yield of 50 to 70% and transthoracic needle-aspiration biopsy has a yield of approximately 75%, whereas mediastinoscopy or mediastinotomy has

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Proportion % (range)</th>
<th>Suggestive Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non–small-cell lung cancer</td>
<td>50 (43–59)</td>
<td>History of smoking; often age &gt;50 yr</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>22 (7–39)</td>
<td>History of smoking; often age &gt;50 yr</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>12 (1–25)</td>
<td>Adenopathy outside the chest; often age &lt;65 yr</td>
</tr>
<tr>
<td>Metastatic cancer†</td>
<td>9 (1–15)</td>
<td>History of malignant condition (usually, breast cancer)</td>
</tr>
<tr>
<td>Germ-cell cancer</td>
<td>3 (0–6)</td>
<td>Usually, male sex and age &lt;40 yr; elevated levels of β human chorionic gonadotropin or alpha-fetoprotein are common</td>
</tr>
<tr>
<td>Thymoma</td>
<td>2 (0–4)</td>
<td>Characteristic radiographic appearance on the basis of the location of the thymus; frequently associated with the parathymic syndromes (e.g., myasthenia gravis and pure red-cell aplasia)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>1 (0–1)</td>
<td>History of asbestos exposure</td>
</tr>
<tr>
<td>Other cancers</td>
<td>1 (0–2)</td>
<td></td>
</tr>
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* Data are from Armstrong et al.,3 Yellin et al.,4 Schraufnagel et al.,5 Chen et al.,13 Rice et al.,15 Nicholson et al.,16 and Detterbeck and Parsons.17
† Approximately two thirds of the patients who have metastatic cancers have breast cancer.
a diagnostic yield of more than 90%. Particular-ly in the case of lymphoma, adequate tissue is needed to characterize the nodal architecture and cell type, and also for immunohistochemistry in order to confirm the subtype.

Although some studies suggest a higher rate of complications from mediastinal procedures among patients who have the superior vena cava syndrome than among those who do not, other studies report low rates of complications even in the presence of the superior vena cava syndrome. A review involving 319 patients with the superior vena cava syndrome found major hemorrhage (not specifically defined) in 3% of patients undergoing mediastinoscopy or mediastinotomy. Bronchoscopy (both fiberoptic and rigid) was associated with low risk (risk of bleeding, 0.5%; and risk of respiratory distress, 0.5%).

**MANAGEMENT**

Management of the superior vena cava syndrome associated with malignant conditions involves both treatment of the cancer and relief of the symptoms of obstruction. Most data regarding management of the superior vena cava syndrome are from case series; randomized trials are scarce. The median life expectancy among patients with obstruction of the superior vena cava is approximately 6 months; but estimates vary widely according to the underlying malignant conditions. Survival among patients presenting with obstruction of the superior vena cava associated with malignant conditions does not appear to differ significantly from survival among patients with the same tumor type and disease stage without obstruction of the superior vena cava. In some patients, treatment of the superior vena cava syndrome and their malignant conditions results in the cure of both.

Management is guided by the severity of the symptoms and the underlying malignant conditions as well as by the anticipated response to treatment. For example, in patients with lymphoma, small-cell lung cancer, or germ-cell tumors, the clinical response to systemic chemotherapy alone typically is rapid. In the majority of patients with non–small-cell lung cancer, relief of symptoms of obstruction of the superior vena cava results from treatment of the cancer (chemotherapy for patients with stage IV disease, and chemotherapy with radiotherapy for those with stage III disease), but the degree and rapidity of response are somewhat less than in patients with lymphoma, small-cell lung cancer, or germ-cell tumors.

**Supportive Care and Medical Management**

An obvious therapeutic maneuver is to elevate the patient’s head to decrease the hydrostatic pressure and thereby the edema. There are no data documenting the effectiveness of this maneuver, but it is simple and without risk. Glucocorticoid therapy (dexamethasone, 4 mg every 6 hours) is commonly prescribed, although its effects have not been formally well studied, and there are only case reports to suggest the benefit. Glucocorticoids reduce the tumor burden in lymphoma and thymoma and are therefore more likely to reduce the obstruction in patients with lymphoma or thymoma than in those with other types of tumor. Loop diuretics are also commonly used, but it is unclear whether venous pressure distal to the obstruction is affected by small changes in right atrial pressure. In an observational study involving 107 patients with the superior vena cava syndrome due to various causes, the rate of clinical improvement (84% overall) was similar among patients receiving glucocorticoids, diuretics, or neither therapy.

### Table 2. Symptoms and Signs Associated with the Superior Vena Cava Syndrome.

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency</th>
<th>Range percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial edema</td>
<td>82</td>
<td>60–100</td>
</tr>
<tr>
<td>Arm edema</td>
<td>46</td>
<td>14–75</td>
</tr>
<tr>
<td>Distended neck veins</td>
<td>63</td>
<td>27–86</td>
</tr>
<tr>
<td>Distended chest veins</td>
<td>53</td>
<td>38–67</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>20</td>
<td>13–23</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>2</td>
<td>0–3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>54</td>
<td>23–74</td>
</tr>
<tr>
<td>Cough</td>
<td>54</td>
<td>38–70</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>17</td>
<td>15–20</td>
</tr>
<tr>
<td>Stridor</td>
<td>4</td>
<td>0–5</td>
</tr>
<tr>
<td>Syncope</td>
<td>10</td>
<td>8–13</td>
</tr>
<tr>
<td>Headaches</td>
<td>9</td>
<td>6–11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>2–10</td>
</tr>
<tr>
<td>Confusion</td>
<td>4</td>
<td>0–5</td>
</tr>
<tr>
<td>Obtundation</td>
<td>2</td>
<td>0–3</td>
</tr>
</tbody>
</table>

*Data are from Armstrong et al., Yellin et al., Schraufnagel et al., Chen et al., Rice et al., and Urruticochea et al.*
In patients with obstruction of the superior vena cava resulting from intravascular thrombus associated with an indwelling catheter, removal of the catheter should be considered. Removal of the catheter is performed in conjunction with anticoagulation therapy (see Areas of Uncertainty).

Radiotherapy
Radiotherapy is often used to treat symptomatic patients with malignant obstruction of the superior vena cava; its use requires a tissue diagnosis. The majority of the tumor types causing the superior vena cava syndrome are sensitive to radiotherapy. A systematic review found complete relief of the symptoms of obstruction of the superior vena cava in 78% of patients with small-cell lung cancer and 63% of those with non–small-cell lung cancer at 2 weeks. Improvement is often apparent within 72 hours.\(^1,3\)\(-5, 11, 16, 31\)\(-35\)

However, objective measures of the change in vena caval obstruction have not paralleled measures of symptomatic improvement based on patients’ reports. In a case series of patients receiving radiotherapy (in most patients as the sole therapy), complete relief of vena caval obstruction as measured on serial venograms was noted in 31% of the patients and partial relief in 23% of the patients. In autopsy studies, complete patency was found in only 14% of the patients and partial patency was found in 10% of the patients, despite reported relief of symptoms in 85% of the patients.\(^11\) These findings suggest that the development of collateral circulation may contribute to improvement of symptoms and underscore the uncertain value of urgent initiation of radiotherapy before chemotherapy is initiated in those patients with chemotherapy-sensitive tumors.

If radiation is given as the initial treatment, the fields should encompass gross disease and the adjacent nodal regions, taking into account the volume of pulmonary and cardiac tissue to minimize complications. CT-based simulation (for designing radiotherapy fields) and irradiation in daily fractions of 1.8 to 2.0 Gy are recommended for the majority of lymphomas. The total dose of radiation should be based on a multidisciplinary plan that incorporates systemic chemotherapy, either from the beginning of treatment or after a brief initial course of radiotherapy. A similar initial course of radiotherapy is often used to treat small-cell and non–small-cell lung cancer, with higher daily fractions of 2.0 to 3.0 Gy. The size and

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**Figure 2. Chest Radiograph and PET–CT Scans of a Patient with the Superior Vena Cava Syndrome.**

Panel A shows a chest radiograph of a patient with the superior vena cava syndrome caused by small-cell lung cancer. Panel B shows a PET–CT scan (CT without contrast) of the same patient. Panel C shows a PET–CT scan (CT without contrast) after the patient had undergone 5 weeks of systemic chemotherapy. The arrow identifies the superior vena cava — an identification that is challenging without contrast enhancement.
configuration of the field may be altered after the administration of several fractions, as symptoms begin to subside and the staging and plans for subsequent management are organized. When the radiotherapy is palliative, the course of treatment is typically over a period of 1 to 3 weeks, with daily fractionation.

**Systemic Chemotherapy**

Complete relief of symptoms of vena caval obstruction is achieved with chemotherapy in approximately 80% of patients with non-Hodgkin’s lymphoma or small-cell lung cancer and in 40% of those with non–small-cell lung cancer.\(^5,27,30,32\) A review of 2 randomized studies and 44 observational studies concluded that among patients with lung cancer, there was no clinically significant difference in the rate of relief from the superior vena cava syndrome whether chemotherapy, radiotherapy, or chemotherapy with radiotherapy was used.\(^30\) In the two randomized trials, there were no significant differences in the rates of relief of symptoms, relapse, or survival with initial chemotherapy alone, as compared with either sequential chemotherapy with radiotherapy among patients with small-cell lung cancer or immediate (concurrent) chemotherapy and radiotherapy among those with non–small-cell lung cancer.\(^32,33\) In observational studies, manifestations of the superior vena cava syndrome caused by other chemotherapy-sensitive malignant conditions such as germ-cell tumors have also been reported to improve rapidly with systemic therapy alone.

**Placement of an Intravascular Stent**

Percutaneous placement of an intravascular stent to bypass the obstruction of the superior vena cava is another possible intervention. Because the stent can be placed before a tissue diagnosis is available, it is a useful procedure for patients with severe symptoms such as respiratory distress that require urgent intervention. Stent placement should also be strongly considered for patients with mesothelioma, which tends not to respond well to chemotherapy or radiation, and may also be particularly useful when obstruction of the superior vena cava is caused by a thrombus associated with an indwelling catheter.\(^36,37\)

Angioplasty for the narrowing of the superior vena cava is generally performed only in preparation for stent placement because of a lack of durable benefit from angioplasty alone.\(^38,39\) Placement of an intravascular stent results in more prompt relief of symptoms than does radiation or chemotherapy (although the usually rapid response to radiation or chemotherapy in patients with tumors sensitive to these therapies means that stent placement is not typically warranted). After stent placement, cyanosis is usually relieved within hours, and edema resolves within 48 to 72 hours in most series (response rate, 75 to 100%). However, in one prospective series, symptoms resolved completely in only 17% of cases. This outcome may have been due to the fact that not all the associated symptoms actually resulted from caval obstruction.\(^26\)

Complications of stent placement have been reported in 3 to 7% of patients with the superior vena cava syndrome, including infection, pulmonary embolus, stent migration, hematoma at the insertion site, bleeding, and, very rarely, perforation. Late complications include bleeding (1 to 14% of patients) and death (1 to 2% of patients) due to anticoagulation, a treatment often recommended after stent placement (see Areas of Uncertainty).\(^16,18,24,25,38-40\)

**Surgery**

Surgical bypass grafting is infrequently used to treat the superior vena cava syndrome. The surgery, which involves a subcutaneous jugular–femoral graft, for example,\(^41\) can be performed with relatively few complications. The more common approach is sternotomy or thoracotomy with extensive resection and reconstruction of the superior vena cava; case series indicate an operative mortality of approximately 5% and patency rates of 80 to 90%.\(^28,42-46\) Thymomas are relatively resistant to chemotherapy and radiation, as compared with lymphomas, and surgery is therefore often appropriate when the superior vena cava syndrome is caused by thymoma. A curative approach generally involves preoperative chemotherapy, surgical resection and reconstruction, and postoperative radiotherapy.\(^15\)

**Durability of Response**

The durability of various treatment strategies appears to be relatively similar and may primarily reflect the underlying malignant conditions. A systematic review found that symptomatic recurrence of the superior vena cava syndrome occurred in
nearly 20% of patients with either small-cell or non–small-cell lung cancer after chemotherapy, radiotherapy, or both. The rate of relapse after stent placement was 11%, although 78% of these relapses were successfully managed by repeat intravascular interventions. Relapse rates ranging from 9 to 20% after stent placement have been reported by others. Rates of occlusion of the superior vena cava of 10% have been reported after surgical reconstruction.

### Areas of Uncertainty

Standardized criteria to grade the severity of symptoms in the superior vena cava syndrome are lacking. The benefit of either short-term or long-term anticoagulation therapy for this syndrome is unclear, although thrombolytic agents have been used effectively in patients with vena caval thrombosis. Most experts recommend anticoagulation after thrombolysis (to prevent disease progression and recurrence) and aspirin after stent placement in the absence of thrombosis, but data to inform these recommendations are limited. Whether the presence of brain metastasis should affect management of the superior vena cava syndrome is unclear. Patients with brain metastasis may undergo stent placement because of the potential of the superior vena cava syndrome to exacerbate cerebral edema, but at least temporary anticoagulation is needed and associated cerebral hemorrhage has been reported. The care of patients with both the superior vena cava syndrome and significant airway obstruction is also unclear. Some authors suggest resection of the tumor mass (complete or subtotal resection) in such patients to provide immediate relief of both clinical problems. The optimal management of recurrent obstruction of the superior vena cava is also controversial. Placement of a stent is often considered because of the limited benefit or the risk of excessive toxic effects from repeat chemotherapy or radiation, but data to guide decision making are limited.

### References


### Guidelines from Professional Societies

There are no formal professional guidelines addressing the management of obstruction of the superior vena cava. A general recommendation supporting consideration of radiotherapy, stent placement for symptomatic obstruction of the superior vena cava due to lung cancer, or both has been made by both the American College of Chest Physicians and the National Comprehensive Cancer Network.

### Conclusions and Recommendations

The superior vena cava syndrome is often clinically striking but rarely requires emergency intervention. The majority of cases are due to malignant conditions; a tissue biopsy is warranted to guide diagnosis and therapy and is generally safe when performed by experienced practitioners. Treatment planning should be multidisciplinary. In patients with life-threatening symptoms or signs of obstruction of the superior vena cava, the placement of an intravascular stent can provide rapid relief. In other patients, such as the patient described in the vignette, information on the tumor type and stage of the cancer should be used to guide the therapy (i.e., chemotherapy or radiotherapy or both or, in occasional cases, surgery alone or in combination with other therapies); these types of therapy can relieve the symptoms of obstruction of the superior vena cava in the vast majority of patients. The presence of the superior vena cava syndrome does not reduce the likelihood of cure of the underlying malignant condition and should not compromise the choice of appropriate therapy.

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

We thank Marilyn L. Powers for assistance in the preparation of the manuscript, Roy H. Decker for assistance in the preparation of the figures, and Waldo Greenspan for his encouragement and support.
A 67-YEAR-OLD MAN RECEIVING HEMODIALYSIS BECAUSE OF KIDNEY FAILURE RESULTING FROM RENOVASCULAR DISEASE WAS ADMITTED TO THE HOSPITAL FOR REVISION OF DIALYSIS ACCESS. SIX MONTHS EARLIER, A DUAL-CHAMBER, PERMANENT PACEMAKER HAD BEEN IMPLANTED IN THE RIGHT SIDE OF THE CHEST FOR THE TREATMENT OF COMPLETE HEART BLOCK. THE DIALYSIS CATHETER, INSERTED INTO THE LEFT INTERNAL JUGULAR VEIN UNDER FLUOROSCOPIC GUIDANCE, SHOWED A LEFT SUPERIOR VENA CAVA DRAINING INTO THE RIGHT ATRIUM THROUGH A CORONARY SINUS. A CHEST RADIOPHOTO SHOWED THE PACEMAKER, WITH LEADS IN THE RIGHT SUBCLAVIAN VEIN AND RIGHT SUPERIOR VENA CAVA, AND A CATHETER IN THE LEFT INTERNAL JUGULAR VEIN AND LEFT SUPERIOR VENA CAVA. SUBSEQUENT DIALYSIS WAS UNEVENTFUL. THE PRESENCE OF A LEFT SUPERIOR VENA CAVA IS THE RESULT OF PERSISTENCE OF THE EMBRYONIC LEFT ANTERIOR CARDINAL VEIN. IT IS PRESENT IN APPROXIMATELY 0.5% OF THE GENERAL POPULATION AND IN 5 TO 10% OF PERSONS WITH OTHER CONGENITAL HEART DEFECTS. IN 90% OF CASES IN WHICH THE LEFT SUPERIOR VENA CAVA IS PRESENT, THERE IS DRAINAGE THROUGH THE CORONARY SINUS INTO THE RIGHT ATRIUM. THE LEFT BRACHIOCEPHALIC VEIN IS USUALLY ABSENT OR ATROPHIC, AND OCCASIONALLY THE RIGHT SUPERIOR VENA CAVA IS ABSENT AS WELL.
The Drenched Doctor

Daniel R. Kaul, M.D., Mark B. Orringer, M.D., Sanjay Saint, M.D., M.P.H., and Stephen R. Jones, M.D.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 55-year-old male physician was seen in August because of a 1-week history of fever and night sweats. The night sweats required at least one nightly change of his pajamas and pillowcase. The patient also noted a persistent cough, which had previously been ascribed to esophageal reflux. There was no sputum production, photophobia, rash, arthralgia, dysuria, or change in bowel function.

Drenching night sweats arouse concern about infections such as tuberculosis and about lymphoma. The presence of fever further suggests an underlying infectious, malignant, or inflammatory disease. The cough may point to a pulmonary cause.

Three months earlier, he had received empirical treatment with a 5-day course of clarithromycin for fever and cough, with initial resolution of the fever and improvement, but not resolution, of the cough. The chest radiograph at that time revealed no infiltrate. There were calcified nodules, 2 to 4 mm in diameter, near the hilum of each lung and a densely calcified hilar lymph node, 2 cm in diameter (Fig. 1). These findings had been noted on chest radiographs over the previous 30 years and attributed to healed histoplasmosis, since the patient had lived in Missouri and Iowa until his mid-20s. He had a history of gastroesophageal reflux disease and 2 years earlier had received a diagnosis of Barrett’s esophagus just above the gastroesophageal junction. At the same time, an ulcer was found just proximal to the gastroesophageal junction; subsequent regular examinations of the esophagus demonstrated healing of the ulcer, and biopsies of the Barrett’s esophagus showed no dysplasia. The patient’s medications included omeprazole, acyclovir (for the prevention of lesions from recurrent herpes simplex infection), and propranolol (as prophylaxis for migraine). The patient had no risk factors for infection with the human immunodeficiency virus (HIV) and had had a negative test for the virus 2 years earlier. He had a history of a positive test with purified protein derivative after exposure to tuberculosis during medical training in 1967, for which he had been treated with isoniazid for 1 year. He had traveled by automobile to Missouri, Arkansas, Oklahoma, New Mexico, and Arizona in early June. He had hiked in meadows and cemeteries in the Midwest and visited ancient Native American dwellings in the Southwest. His teeth had been cleaned 2 weeks before the onset of fever.

The cough has lasted longer than 8 weeks and thus can be classified as chronic. One possible cause of the cough is gastroesophageal reflux disease that has not been adequately suppressed by the proton-pump inhibitor. However, the development of fever and night sweats suggests a pulmonary infection or inflammatory disease. The patient’s travels might have exposed him to endemic fungal pathogens such as Histoplasma capsulatum or Coccidioides immitis. Esophageal ulcers may have nonpeptic causes such
as infection with HIV or with other viruses. Treatment with isoniazid reduces, but does not eliminate, the possibility of reactivation tuberculosis. Endocarditis should always be considered in a patient with fever of unknown origin. Routine dental care, however, is common and should not be considered a risk factor for endocarditis in patients without known valvular disease.

Leukopenia occurring in a patient with a nonspecific febrile illness and environmental exposure to ticks in the early summer arouses concern about tickborne illnesses such as Rocky Mountain spotted fever or human monocytic ehrlichiosis; the patient might have acquired such an illness in Arkansas, Missouri, or Oklahoma. Viral illnesses may also cause leukopenia. Given the patient’s past residence in the midwestern United States, the finding of stable calcified pulmonary nodules and hilar nodes is suggestive of past infection with *H. capsulatum*. However, previous infection with *Mycobacterium tuberculosis* or other endemic fungi may also cause this radiographic finding. Thus, histoplasmosis and coccidioidomycosis are now part of the differential diagnosis; either illness may cause leukopenia.

Additional testing — including liver tests, blood cultures, and serologic tests for HIV and for the infectious agents mentioned above — is indicated. In addition, I would suggest computed tomography (CT) of the patient’s chest and abdomen.

Over the next week, the fever and cough continued, and the night sweats increased in severity, drenching the patient’s sheets as well as his nightclothes. He began sleeping on bath towels that had to be changed several times during the night. On several occasions, his temperature was 38.4°C or higher. He had lost 4 lb (1.8 kg). He returned to his physician’s office; an examination showed no abnormalities. The patient’s white-cell count was now 3700 per cubic millimeter, with 32% segmented neutrophils, 13% bands, and 10% monocytes. The hematocrit and platelet count were again normal. The electrolyte levels were normal. The serum creatinine level was 1.0 mg per deciliter (88.4 μmol per liter); aspartate transaminase, 140 U per liter (upper limit of the normal range, 50); alkaline phosphatase, 72 U per liter (upper limit of the normal range, 117); and lactate dehydrogenase, 1321 U per liter (upper limit of the normal range, 618). The results of urinalysis were normal. A blood culture for *Stenotrophomonas*...
maltophilia was positive in the aerobic bottle of one of the two sets.

The growth of S. maltophilia is unexpected. This pathogen is not part of normal human skin flora, and even growth limited to a single blood-culture bottle cannot be easily dismissed as a contaminant. S. maltophilia is typically a hospital-acquired pathogen; risk factors for infection with this organism include prolonged hospitalization and serious underlying disease. Employment in a health care setting has not been reported as a risk factor for disease associated with S. maltophilia. Community-acquired bacteremia involving this organism may occur with profound immunosuppression or undiagnosed cancer (possibly of the gastrointestinal tract). Blood cultures should be repeated before any therapy is administered, and an HIV serologic test should also be performed.

Two more sets of blood cultures revealed no bacterial growth. The previous culture was interpreted as a false positive result, probably due to contamination at the time of a difficult venipuncture. The serologic tests for Treponema pallidum, HIV, brucella, Ehrlichia equi and E. chaffeensis, Borrelia burgdorferi, and hepatitis C virus were negative. A polymerase-chain-reaction assay for ehrlichia was negative. A test for histoplasma urinary antigen was negative. Tests were positive for cytomegalovirus IgG antibody and negative for IgM antibody.

Five days later, 12 days after the first examination, the patient’s white-cell count was 7200 per cubic millimeter, with 21% segmented neutrophils, 29% bands, 1% metamyelocytes, 24% reactive lymphocytes, and 6% monocytes. The platelet count was 100,000 per cubic millimeter, and the platelets were described as large. The erythrocyte sedimentation rate was 27 mm per hour. The results of serum protein electrophoresis were unremarkable.

The negative follow-up blood cultures before any treatment was initiated do suggest that S. maltophilia contaminated the blood-culture bottle. The most useful laboratory finding is the large number of reactive lymphocytes. Common causes of reactive lymphocytes include mononucleosis due to Epstein–Barr virus (EBV) and acute cytomegalovirus infection. Lymphoma, rheumatologic diseases (e.g., lupus), endocrine disorders (e.g., thyrotoxicosis), and drug reactions may also cause reactive lymphocytosis. Older adults, if not infected earlier in life, may acquire EBV-related infectious mononucleosis and have prolonged fever and night sweats. Sore throat and lymphadenopathy are usually present but may not be prominent. Thrombocytopenia (with large platelets indicating autoimmune destruction) and mild abnormalities on liver-function tests are common; neutropenia may also be present. In rare cases, moderate or even severe cough may occur. I would send an infectious mononucleosis heterophile test and specific EBV antibody panel.

CT of the chest (Fig. 2) and abdomen revealed no lymphadenopathy or masses; the scan was interpreted as normal except for the previously recognized calcifications in the lung and lymph nodes of the hilum and mediastinum. A bone marrow biopsy was normal, and stains and cultures for bacteria, fungi, and mycobacteria were negative.

The patient was treated with ciprofloxacin (750 mg twice a day for 10 days). The fever diminished, the patient had a sense of well-being, and the excess of bands resolved, but the fever and night sweats returned after the course of medication had been completed. The cough worsened, and the patient reported that it was exacerbated by swallowing foods and liquids, with paroxysms of coughing when he swallowed fluids. He recalled that for years he had coughed when he ate raw carrots but not when he swallowed other foods or liquids.

The patient has now had two febrile episodes associated with cough that improved with antibi-
otic treatment. In this context, the exacerbation of the cough in conjunction with swallowing suggests recurrent aspiration. The absence of infiltrates on chest imaging makes a case against this possibility, however, and the patient does not have any known anatomical or neurologic condition that would predispose him to aspiration. Another possibility is that a bronchoesophageal fistula has developed. This usually occurs in association with cancer of the esophagus or bronchus; in rare cases, however, it may occur in the setting of infection with *M. tuberculosis* or *H. capsulatum*. Findings on the patient’s chest CT scan suggest previous infection with one of these agents. A barium-swallow examination would be helpful to determine whether a fistula is present.

The patient underwent upper endoscopy because of the suspicion that the cough was related to esophageal reflux. Changes consistent with Barrett’s esophagus were again seen just above the gastroesophageal junction. As the endoscope was removed, bubbles that increased in size and frequency with expiration were seen coming out of the right posterolateral midesophageal wall (Fig. 3).

This finding is consistent with a bronchoesophageal fistula. An esophagogram could be used to confirm and better define the fistula. The fever may be due to recurrent pneumonia or even a contained abscess in the mediastinum. Conceivably, *S. maltophilia* bacteremia could occur in this situation.

A diatrizoate meglumine (Gastrografin) swallow examination was performed; the contrast material entered the mediastinum and the bronchus and then the right lower lobe of the lung (Fig. 4). The soft-tissue mass outlined by the fistulous tract was interpreted as an abscess. Review of the CT scan of the chest did not reveal evidence of an abscess or phlegmon. A week later, surgical exploration of the patient’s chest revealed an inflammatory process, without an abscess, in the mediastinum near the esophageal end of the fistula; pathological analysis revealed nonspecific chronic inflammation. The bronchoesophageal fistula was closed, and a portion of the adjacent ligated azygos vein was interposed between the bronchial and esophageal suture lines. Postoperative laboratory tests showed a normal complete blood count.

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**Commentary**

A fundamental characteristic of expert diagnostic reasoning is the recognition of a key clinical finding, or “pivot point.” This is particularly important in complex cases requiring longitudinal follow-up, such as fever of unknown origin. The classic causes of fever of unknown origin include chronic infection, cancer, and inflammatory diseases.

Unusual causes may also be found, as in this case, which involved several clinical findings or historical clues that the discussant pursued.
These included gastroesophageal reflux disease with Barrett’s esophagus, a history of travel to areas in which various infections are endemic, a positive blood culture for S. maltophilia, and reactive lymphocytosis. Although these findings certainly deserved attention, none rose to the level of true pivot points. In contrast, paroxysms of coughing caused by swallowing fluids did. This was a description of aspiration during the act of swallowing, which warranted immediate evaluation to determine whether laryngeal penetration was occurring, whether there was a mechanical or functional obstruction in the esophagus (e.g., tumor, benign stricture, diverticulum, achalasia, or diffuse spasm), or whether there was communication between the esophagus and tracheobronchial tree. Although a pivot point certainly is not present in every complicated case, the discussant recognized this key finding, which ultimately resulted in the determination of the cause of fever and the surgical cure.

The majority (approximately 80%) of acquired esophagorespiratory fistulas are due to malignant disease of the esophagus or chest; patients typically present with advanced disease, and the fistula is readily detected with the use of a barium-swallow examination. If there is a suspected esophagorespiratory fistula, diatrizoate meglumine (gastrografin) should be avoided, since it may cause a chemical pneumonitis. Nonmalignant causes of esophagorespiratory fistulas are diverse and include chronic infections (e.g., tuberculosis), radiation injury, congenital abnormalities, postsurgical or postprocedural lesions, local injury, and broncholithiasis. Barrett’s esophagus is a rare cause of esophagorespiratory fistulas. In this patient, the most recent endoscopy had shown healing of an ulcer in the distal esophagus, yet the fistula was in the midesophagus. In any case, the distal esophagus is well below the major airways, and a penetrating ulcer at that level would be expected to erode into the pulmonary parenchyma.

The management of a bronchoesophageal fistula is surgical and involves separation of the esophagus from the bronchus, suture repair of the openings in both, and interposition of a viable tissue flap (e.g., of intercostal muscle, rotated mediastinal fat pad, or pleura) to prevent recurrence of the fistula.

Figure 4. Radiograph from a Diatrizoate Meglumine (Gastrografin) Swallow Examination Showing the Extent of the Bronchoesophageal Fistula.

Calcified mediastinal nodes (like those seen on our patient’s chest film) are usually due to granulomatous diseases and are commonly seen in patients residing in areas where histoplasmosis or tuberculosis is endemic. We determined that our patient did not have active histoplasmosis or tuberculosis, given the negative antigen test, absence of growth of H. capsulatum in the bone marrow–biopsy specimen, absence of granulomatous inflammation in the surgical specimen, and long-term clinical improvement after surgery. However, the radiologic finding of a heavily calcified mediastinal lymph node in our patient shows the probable cause of the esophagorespiratory fistula.

The pathophysiological characteristics of acquired esophagorespiratory fistulas due to quiescent granulomatous disease are readily understood with knowledge of mediastinal anatomy. In the upper and middle mediastinum, the esophagus is located posterior to the trachea. Lymph nodes may become inflamed and enlarged owing to histoplasmosis or tuberculosis. The inflamed lymph nodes adhere to the adjacent esophageal wall. As
healing progresses, scarring and contracture of the lymph node pull out a small area of adjacent esophageal wall, thereby creating a traction diverticulum,\textsuperscript{10} which is typically about 1 cm in diameter and asymptomatic. The calcified lymph node adheres to both the esophageal diverticulum and the airway. Over time, with mediastinal movement and local erosion, an esopha-gorespiratory fistula may develop. Depending on the location of this process, the result may be a tracheoesophageal fistula, a bronchoesophageal fistula, or a fistula between the esophagus and the adjacent lung parenchyma.\textsuperscript{9}

The recognition of the pivot point — coughing on swallowing — in this case of a rare but dramatic cause of fever of unknown origin was required for the correct diagnosis. The case underscores the importance of continued questioning for new symptoms in complex diagnostic cases, as one of the authors of this article (who was the drenched doctor in question) can attest.

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\textbf{REFERENCES}


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Bisphosphonates are an important option for the prevention of fractures in postmenopausal women. However, the complex instructions for the administration of oral bisphosphonates are inconvenient or unsuitable for many patients, and adherence to long-term therapy is poor. The introduction of oral regimens for administration once weekly and, recently, once monthly has been associated with improved tolerability for patients, although adherence remains suboptimal. The demonstration that once-yearly intravenous infusions of zoledronic acid produced a sustained reduction in bone turnover and increased bone mineral density raised the prospect that even less frequent administration and the hope of better adherence might be realized. Now, the potential strengths of this treatment regimen are further supported by evidence that once-yearly infusions of zoledronic acid are associated with a reduction in fractures in postmenopausal women with osteoporosis, as reported by Black et al. in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) (NCT00049829) study in this issue of the Journal.

The efficacy data from the HORIZON study are impressive. At 3 years, vertebral fractures were reduced by 70%, hip fractures by 41%, and nonvertebral fractures by 25%. Although a direct comparison with other treatments cannot be made in the absence of head-to-head studies of fracture outcome, the magnitude of effect appears to be at least similar to and possibly better than (in the case of vertebral fractures) that reported for other interventions. More important, the data indicate a broad spectrum of antifracture efficacy extending across nonvertebral fractures and including those at the hip. The study was adequately powered to demonstrate these reductions in fractures. Of the 7765 women who underwent randomization, 84% remained in active follow-up throughout the 3-year trial period. In particular, the mean age of women in this study (73 years) and the inclusion of women until the age of 89 years ensured that the number of hip fractures (88 in the placebo group vs. 52 in the zoledronic acid group) was sufficient to allow for a demonstration of efficacy at this key site.

No excess of deaths was seen in the treatment group. The increased frequency of symptoms reflecting an acute-phase reaction after infusion of zoledronic acid is to be expected (the reported events occurred mainly after the first infusion), and the absence of long-term adverse effects on renal function is reassuring. However, the significant increase in atrial fibrillation as a serious adverse event associated with zoledronic acid treatment was unexpected, particularly since the majority of these events occurred more than 30 days after infusion and therefore could not be attributed to early, transient hypocalcemia. The increased frequency of atrial fibrillation was not observed in a small electrocardiographic substudy, nor did it translate into an excess rate of death from cardiovascular causes. A letter in this issue of the Journal indicates a trend toward serious adverse events involving atrial fibrillation after alendronate treatment, an observation that also bears further study. Thus, it is a potential concern, and a causal relationship must be given serious consideration. For this reason, safety data from ongoing
clinical trials of zoledronic acid are awaited with interest.

Although the association of osteonecrosis of the jaw with bisphosphonate therapy has been reported mainly in patients with cancer who were receiving high total doses, the possible occurrence of this adverse event during therapy for osteoporosis has created sufficient anxiety to change clinical practice in some parts of the world. Because the association has been recognized only recently, its frequency has not been evaluated in prospective clinical trials. Thus, it is reassuring that despite adjudication and expert review of possible symptoms or signs of osteonecrosis of the jaw in the HORIZON study, only two potential cases were identified, and both subsequently resolved with appropriate therapy. Since one of the affected women was in the placebo group, these results provide no evidence for a specific association between osteonecrosis of the jaw and zoledronic acid in the doses used for treatment of osteoporosis in postmenopausal women. The findings also emphasize that the condition may develop in the absence of current bisphosphonate therapy. Of possible relevance to this issue, the degree of suppression of bone turnover that is induced by zoledronic acid, as assessed with the use of biochemical markers, was similar in the study by Black et al. to that reported with other bisphosphonates.

Of the currently available options for the treatment of osteoporosis, only alendronate, risedronate, and strontium ranelate have a spectrum of antifracture efficacy similar to that shown for zoledronic acid. Therefore, these drugs can be regarded as front-line options for the majority of postmenopausal women at high risk for fracture. In clinical practice, the choice of treatment will depend on a number of factors, including the preference of patients. Whereas the once-yearly regimen of zoledronic acid is likely to be attractive to some women, the need for intravenous infusion may deter others, particularly in regions where such administration would have to be provided in secondary care settings rather than in primary care offices. Intravenous zoledronic acid may be particularly appropriate for women who are admitted to the hospital with a fracture (especially a hip fracture), for whom the first infusion could be given during their hospital stay. In addition, among the growing population of very elderly women with osteoporosis, oral bisphosphonates are unsuitable for a substantial minority, and zoledronic acid may provide a potential alternative for these women. The only intravenous bisphosphonate approved for osteoporosis is ibandronate, which is administered every 3 months as a single intravenous (“push”) injection during a period of 15 to 30 seconds, but robust evidence for a reduction in nonvertebral fractures after the administration of ibandronate is lacking.

Despite the availability of effective treatments for osteoporosis, poor adherence to drug regimens reduces the benefit and presents a major challenge for health professionals. Intravenous administration ensures that treatment is correctly delivered and avoids the stringent administration instructions required for oral bisphosphonates. In the case of zoledronic acid, even a single infusion appears to ensure efficacy for at least 1 year and probably longer. The practicality and acceptability of annual intravenous therapy in large numbers of women remain to be tested. Nevertheless, increased treatment choices for patients are to be welcomed and may provide one means of improving adherence and treatment outcomes in osteoporosis.

Dr. Compston reports serving on advisory boards for Procter & Gamble, Servier, Nycomed, Shire, and Crescent Diagnostics; receiving speaking fees from Procter & Gamble, Nycomed, Servier, Shire, and Eli Lilly; serving on data and safety monitoring boards for Novartis and Amgen; receiving research grants from Procter & Gamble and Servier; and having served as an expert witness in medicolegal and patent disputes related to alendronate. No other potential conflict of interest relevant to this article was reported.

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2. Compston JE, Seeman E. Compliance with osteoporosis therapy is the weakest link. Lancet 2006;368:973-4.
Beyond Epicardial Reperfusion

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The pathogenesis of an acute myocardial infarction consists of the rupture of atherosclerotic plaque, followed by a sudden thrombotic coronary occlusion. Pioneering studies performed more than 40 years ago, even before there was full recognition of the underlying pathobiology, showed that nonselective intracoronary fibrinolysis can restore perfusion to the jeopardized vascular territory. Primary percutaneous coronary intervention (PCI) has now emerged as the optimal mode of reperfusion therapy, if performed by an experienced team within 90 minutes after the first medical contact. Primary PCI results in patency of the occluded artery in almost all patients and in normalization of epicardial perfusion, according to Thrombolysis in Myocardial Infarction (TIMI) grading, in more than 90% of patients.

Despite the general success of primary PCI, approximately 15% of patients have inadequate myocardial perfusion in the absence of angiographic evidence of mechanical vessel obstruction. This “no-reflow” phenomenon may be due to microvascular damage after myocardial ischemia, to cell necrosis and regional inflammatory responses induced by reperfusion, or to both. In addition, microvascular obstruction may be caused by the embolization of atheromatous and thrombotic debris, either spontaneously or after mechanical dilation of the culprit lesion. This inadequate myocardial perfusion is clinically relevant, since it is associated with larger myocardial infarcts, greater impairment of left ventricular function, and a worse clinical outcome than those in patients with adequate perfusion.

These clinical observations have led to intensive research on the salvage of viable myocardium with the use of adjuvant pharmacologic therapy in the setting of primary PCI. The Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial showed a favorable clinical outcome when platelet aggregation was inhibited with the use of a glycoprotein IIb/IIIa inhibitor, if administered before primary stent implantation in the coronary artery. In daily clinical practice, an antiplatelet and anticoagulation regimen consisting of aspirin, clopidogrel, and heparin serves as standard adjuvant pharmacotherapy in patients undergoing primary PCI, whereas the administration of a glycoprotein IIb/IIIa inhibitor is recommended in patients showing poor ST-segment resolution or evidence of a no-reflow phenomenon.

Mechanical thrombectomy and embolic protection devices are logical therapeutic approaches to treat or prevent microembolization. However, randomized trials have failed to show a beneficial effect of these devices on myocardial reperfusion, infarct size, or clinical outcome. The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) (NCT00168792) trial tested the use of adjuvant fibrinolytic therapy with tenecteplase before primary PCI. This trial was stopped prematurely owing to a higher incidence of cardiac complications and stroke in the tenecteplase group than in the group that did not receive tenecteplase. Consequently, the optimal aggressive pharmacologic strategy to be used as an adjunct to primary PCI remains undefined.

In this context, the study by Sezer et al. in this issue of the Journal is of particular interest. The investigators evaluated the effect of intracoronary streptokinase immediately after successful PCI on myocardial perfusion in patients who also received a standard medical regimen including aspirin, heparin, clopidogrel, and a glycoprotein IIb/IIIa inhibitor. The local administration of streptokinase has the advantage over systemic fibrinolytic...
therapy of inducing adequate fibrinolysis at the site of injury while placing the patient at lower risk for bleeding complications. The patients randomly assigned to receive streptokinase showed improved myocardial perfusion, according to traditional angiographic measures such as the corrected TIMI frame count and the myocardial blush grade. Moreover, these angiographic findings coincided with reduced microvascular resistance, as assessed with the use of intracoronary pressure and temperature measurements and transthoracic Doppler echocardiography. However, these positive angiographic and hemodynamic findings did not reflect better preservation of left ventricular function, as assessed with the use of echocardiography and single-photon-emission tomography (SPECT).

The evaluation of the effect of coronary interventions on the hemodynamics of the microvasculature is still terra incognita, considering the limited number of studies performed in dedicated centers.\textsuperscript{9,10} Intracoronary diagnostic techniques involving sensor-equipped guidewires are well suited for evaluation of the dynamics of the coronary microvasculature. Results from initial clinical invasive studies have confirmed experimental observations and findings from positron-emission tomography performed in humans.\textsuperscript{11,12} Distal microvascular resistance is largely heterogeneous in the absence of epicardial narrowings, not only between patients but also between neighboring vascular territories. This interpatient and intrapatient variability of microvascular resistance is reduced, but still present, during conditions of hyperemia. The resistance of the dilated microvascular bed also depends on pressure and, therefore, is influenced by the presence of a coronary stenosis or the relief of a pressure gradient after successful PCI. An appropriate interpretation of the complexity of the coronary microvasculature ideally requires a combination of intracoronary pressure and flow-velocity measurements.\textsuperscript{13} Moreover, to account for the interference of epicardial resistance and the interpatient and intrapatient variability of microvascular resistance, study patients should preferably serve as their own controls.

The invasive measurements in the study by Sezer et al. were performed 2 days after PCI, without a comparison with measurements immediately after PCI or at follow-up. Therefore, the main conclusion of this study, that intracoronary streptokinase reduces microvascular resistance, has to be interpreted with caution, since it is based on a comparison between patients randomly assigned to one of two groups rather than on an intrapatient analysis. In addition, the evaluation of intra-
coronary hemodynamic variables was based on data derived from pressure and temperature measurements rather than on simultaneous pressure and flow-velocity measurements. Nevertheless, the uniform results of the various invasive and noninvasive techniques applied by Sezer et al. for evaluation of the coronary microvasculature provide support for their conclusions.

Remarkably, the reduction of microvascular resistance, which is probably due to the destruction of microemboli, was not associated with improved myocardial function. Left ventricular remodeling is a multifactorial process that probably requires a broader therapeutic approach than just the dissolution of microemboli; it should probably also include the reduction of the inflammatory response after myocardial infarction. The limited number of patients studied by Sezer et al. may preclude an interpretation of the effect of streptokinase on the final size of the myocardial infarct and on regional left ventricular function. For this purpose, magnetic resonance imaging with contrast enhancement may be more sensitive than echocardiography and SPECT. In addition, approximately 20 to 30% of the small number of patients studied had a nonanterior myocardial infarction. The nonuniform selection of patients may have helped obscure the effect of streptokinase on regional left ventricular hemodynamics. On the other hand, the results of the study by Sezer et al. do not suggest that the intracoronary administration of streptokinase has harmful effects, such as hemorrhagic expansion of an infarct.

Sezer et al. are to be commended for conducting this interesting, hypothesis-generating study showing that the intracoronary administration of streptokinase after primary PCI exerts a beneficial effect on the coronary microvasculature. The use of intracoronary fibrinolysis for myocardial reperfusion can be considered a pendulum swing, given the pioneering studies performed decades ago and the fact that intracoronary streptokinase had almost disappeared from the therapeutic armamentarium. In view of their clinical relevance, the findings of Sezer et al. warrant further analysis in larger-scale clinical studies aimed at a multifactorial therapeutic approach to minimizing reperfusion injury. Sensitive noninvasive and invasive diagnostic techniques should be used to evaluate the potential of this new approach as an adjunct to our current therapeutic strategy in patients with an acute myocardial infarction.

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

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Medicare Spending on Physicians — No Easy Fix in Sight
Joseph P. Newhouse, Ph.D.

Medicare’s method of payment to physicians has been a thorny problem since the program began more than 40 years ago. Medicare’s initial method for setting fees mimicked the typical system used by the Blue Shield plans of the 1960s: payment for the lowest of usual, customary, or reasonable fees. Twenty-five years later, the resulting fee schedule made little sense; individual physicians were paid grossly different amounts for providing identical medical services, with large variations across different geographic areas. As a result, Medicare adopted the resource-based relative-value scale in an attempt to tie relative fees to the amount of work and practice expense involved in delivering specific services. Henceforth, Congress would simply determine the dollar value of a unit on this scale; the Centers for Medicare and Medicaid Services would determine the relative value of each service.

The resource-based relative-value scale was introduced amidst a widespread view that physicians who performed evaluation and management services were underpaid as compared with those who performed procedures, in part because physicians performing new procedures tended to become more adept at them over time, and therefore the cost per procedure decreased (alternatively, physicians could perform more such procedures in a day). A similar scenario was less plausible for evaluation and management services. Medicare fees, however, often did not decrease commensurately with any reduction in cost. As a result, many procedures were thought to have become highly remunerative and perhaps were performed too often as a result. Moreover, there was some concern that the underpayment for evaluation and management services was leading to a dearth of primary care physicians.

Perhaps surprisingly to those involved in the initial reform, the concerns about potential underpayment for evaluation and management services have persisted, along with concerns that this underpayment has contributed to a shortage of primary care physicians. In this issue of the Journal, Maxwell et al. examine how the distribution of payments under Medicare’s fee schedule changed over the decade from 1992, when it was introduced, through 2002. They show that, as the reformers intended, the relative values or fees for evaluation and management services increased 20%, whereas those for imaging, major procedures, and other procedures decreased 1 to 15%.

Despite the fee increase, Maxwell and colleagues report that in 2002 the share of Medicare spending on physicians for evaluation and management was exactly where it was in 1992 — 49.5%. How could this be, given the large increase in relative fees? Considering just the service codes that existed in 1992, the quantity of evaluation and management services grew 18% over the following decade, but the quantity of imaging services soared some 70% and the quantity of nonmajor procedures increased 21%. Thus, the disproportionate increase in the quantity of imaging services offset the relative increase in the fees for evaluation and management services. Moreover, Maxwell et al. show that almost a quarter (10.4% of 44.9%) of the growth in the total quantity of physicians’ services was attributable to the introduction of new codes, few of which were for evaluation and management services, since new codes are much more likely for imaging, procedures, and tests.

However, if the fee Medicare pays actually reflects the resources used in evaluation and management services — the intent of the resource-based relative-value scale method — why do so many primary care physicians feel shortchanged? Among the reasons is a formula that Congress has used since 1998 to limit the growth in spending on physicians’ services per Medicare beneficiary to approximately the rate of growth in the gross domestic product. Because of this limit, spending for evaluation and management services is reduced to accommodate the surges in imaging services and new codes. In fact, for the past 6 years, the formula has indicated that fees should be cut. Since 2003, Congress has ignored the formula, but it has either given below-inflation increases or simply frozen fees. The net result is that Medicare payments to physicians for evaluation and management services have not increased.

The data described by Maxwell et al. also point to a second explanation for why payments for evaluation and management services have not been higher. Although the resource-based relative-value scale may have better aligned fees with costs than
the old method based on the Blue Shield system, the cost of new procedures often decreases over time. In principle, any such decreases are to be accounted for by an annual review of relative fees and a more intensive 5-year review, but in practice this mechanism has been flawed. Initial errors should have been equally likely to have been high or low, so correcting them should have led to roughly equal numbers of fee increases and decreases. Since new procedures generally become less costly to perform as they become part of routine practice, on balance the reviews should have decreased more fees than they increased. Maxwell and colleagues, however, show that exactly the opposite happened. Relative fees are almost never reduced in the review process and are frequently increased; they rose fully 82% of the time in the first 5-year review. This increase probably stems from the “squeaky wheel syndrome” — services that are relatively undervalued are more likely to generate complaints and hence enter the review process than services that are overvalued. Although the overall spending limit prevents such asymmetric changes from generating increases in Medicare spending on physicians, the net result may well be a distorted relative-value scale.

Unfortunately, neither the spending limits nor the asymmetric review process is likely to disappear. The overall pressure on the federal budget and the large share of it that Medicare represents, 17% in 2007, will probably keep the increases in Medicare spending on physicians’ services modest. Many procedures that become less costly over time may well continue to fly under the radar of the review process. With no easy fix in sight, Medicare spending on physicians will probably remain a thorny issue.

Dr. Newhouse reports serving on the board of directors of and holding equity in Aetna. No other potential conflict of interest relevant to this article was reported.

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Mammographic Breast Density

TO THE EDITOR: Boyd and colleagues (Jan. 18 issue) report a case–control study, nested within data derived from previous cohort studies, that strongly supports breast density as a risk factor for breast cancer. However, using only 1 matched control for the analysis, in spite of the identification of 10 potential controls for each case, limited the statistical conclusions. In addition, it is not clear how the breast cancers were ultimately discovered. If the majority of the cancers were eventually diagnosed on mammography, then despite the delay in diagnosis, annual mammography remains a valuable screening tool even in women with dense breast tissue.

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TO THE EDITOR: Boyd and colleagues (Jan. 18 issue) report a case–control study, nested within data derived from previous cohort studies, that strongly supports breast density as a risk factor for breast cancer. However, using only 1 matched control for the analysis, in spite of the identification of 10 potential controls for each case, limited the statistical conclusions. In addition, it is not clear how the breast cancers were ultimately discovered. If the majority of the cancers were eventually diagnosed on mammography, then despite the delay in diagnosis, annual mammography remains a valuable screening tool even in women with dense breast tissue.

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TO THE EDITOR: There is probably some relationship between the density of breast tissue and the risk of breast cancer, but the methods used by Boyd and colleagues preclude the emphasis that they and others place on this relationship, for several reasons. First, three-dimensional tissue-volume ratios cannot be quantitatively derived from two-dimensional mammographic images in the absence of values for the compressed thickness of the breast and half-value layers. Second, radiologists cannot determine true volume ratios. Third, computer algorithms allow reproducible segmentation of two-dimensional pictures but cannot predict three-dimensional volumes. Fourth, use of the craniocaudal mammographic view alone excludes much of the breast (which is the denominator in the volume ratio). Fifth, on two-dimensional imaging, there is no definition of where the breast ends, and there is considerable variability in how the breasts are positioned, making accurate calculation of the tissue-volume ratio impossible. I have seen cases in which same-day repositioning of the breast halved the measured percentage of tissue density. Finally, it is not possible to establish whether biases are systematic and will wash out with large numbers of cases. Before strong conclusions can be made about the relationship between breast-tissue density and the risk of breast cancer, more accurate data must be obtained. Preferably, three-dimensional imaging techniques such as magnetic resonance imaging, computed tomography, or digital breast tomosynthesis should be used.

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TO THE EDITOR: Boyd and colleagues provide much useful information about the relationship between breast density and the risk of breast cancer. However, using only 1 matched control for the analysis, in spite of the identification of 10 potential controls for each case, limited the statistical conclusions. In addition, it is not clear how the breast cancers were ultimately discovered. If the majority of the cancers were eventually diagnosed on mammography, then despite the delay in diagnosis, annual mammography remains a valuable screening tool even in women with dense breast tissue.

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mammographic density and the risk of breast cancer. However, the comparison of attributable risks for women at different ages with the use of a fixed threshold may be confounded by the lower breast density in general in older women. Age-specific risks (and risks specific to the body-mass index) are needed for different density values. Mammographic density is an enrollment criterion for the International Breast Cancer Intervention Study II, along with other factors. Learning how to combine these factors in an optimal way is a priority for prevention research.

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TO THE EDITOR: Boyd et al. do not indicate that the positive correlation between mammographic breast density and the risk of breast cancer is independent of the method used to detect the cancer. They do not mention intergroup assessment of pain or the use of analgesics or compressive forces. Women with dense breasts often experience pain while undergoing mammography. Pain is a universal warning sign of tissue damage and may be associated with an increased risk of breast cancer, yet women who experience severe pain during mammography are often advised to override this warning sign with the use of medication or by other means.

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THE AUTHORS REPLY: Dandolu and Hernandez point out that the statistical power of our study could have been increased with the use of more than one randomly selected control subject per case subject. However, the levels of statistical significance shown in our report do not suggest that lack of power was a limiting factor. Mammography was the only method used at screening in one program in our study and was the predominant method in the other two programs, and more than half the cancers that developed in women with extensive mammographic density were detected at screening.

We have previously noted the limitations of existing methods of assessing mammographic density referred to by Kopans. None of those methods take breast thickness into account and are thus based on the projected area, rather than on the volume of breast tissue. Current computer-assisted methods of measurement require a dichotomous threshold between dense and nondense tissue, and uncontrolled sources of variation, in positioning, exposure, and processing, may be present. However, in prospective studies such as ours in which mammography is used 1 to 8 years before diagnosis, these sources of error are expected to affect equally women in whom breast cancer will develop and those in whom it will not and to attenuate estimates of risk. We may thus be underestimating the true underlying risk of breast cancer associated with mammographic density.

Notwithstanding these limitations, as discussed by Kerlikowske and shown in a recent systematic review, there is now a substantial body of consistent evidence showing that the relative risks of breast cancer associated with mammographic density, as currently measured, are greater than for most other risk factors for this disease; that these risks persist after adjustment for other risk factors and, as we show, over time; and that they are present for both breast cancers detected by screening and those not detected by screening. Studies of the limitations of existing methods of measurement may further increase risk estimates.

Cuzick points out that the attributable risk (which we report) and the predictive value are different measures of the importance and usefulness of a risk factor. It is unlikely that the number of subjects in the present study is large enough to provide precise estimates specific to age and body-mass index.

In response to van Netten et al., who raise the interesting question of whether pain during mammography may be a risk factor for breast cancer, we are not able to examine this issue with the available data.
A Gene Signature in Breast Cancer

TO THE EDITOR: Liu et al. (Jan. 18 issue)\(^1\) report on a 186-gene “invasiveness” gene signature (IGS) that discriminates between normal breast epithelium and tumorigenic breast-cancer cells that are characterized by CD44 expression and low or undetectable levels of CD24. This signature is associated with survival among patients with breast cancer. We profiled 200 breast tumors with the use of DNA microarrays and determined their molecular subtype. We used the 186-gene IGS to classify the basal and the luminal samples. The two subtypes were well separated. We found that 89% of genes that were overexpressed in cancer stem cells were coordinately overexpressed in basal samples. This association provides a link between an intrinsic feature of breast cancers (basal subtype) and cancer stem cells, reinforcing the relevance of the 186-gene IGS. The result suggests that basal-cell breast cancers are enriched in tumorigenic breast-cancer stem cells or maintain a similar transcriptional profile owing to a block of differentiation, which partially explains the poor prognosis for patients with such tumors.

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TO THE EDITOR: Liu et al. conclude that the 186-gene IGS they developed is new, since it shows little overlap with other breast-cancer signatures. However, the IGS they discuss is similar to a “genetic grade” signature defined and characterized by Ivshina et al. in a data set from more than 400 patients.\(^2\) Both signatures seem to be prognostic for tumors of intermediate grade only. To address this issue, we tested the independence of the IGS and the 264 genes identified by Ivshina et al., further motivated by a recent article suggesting dependency among several breast-cancer signatures in spite of little overlap.\(^2\) On the basis of our data, the IGS and 264 genetic-grade classifiers had a correlation of 0.81 (P<0.001) and were in agreement on the classification of 85% of tumors (Fig. 1). Since the 264-gene signature is largely a proliferation marker,

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ruling out dependency on proliferation now seems to be important in demonstrating the novelty of the IGS.

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To the Editor: Liu et al. report that the status of the estrogen receptor and differentiation in tumors outperformed the prognostic value of the IGS among patients in their study. We suggest that their data may be limited by both the paucity of samples from which this signature was derived and the heterogeneous histologic features, tumor origin, and treatment. The current findings should be validated before incorporating this signature into clinical trials.

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The authors reply: We agree with Bertucci and colleagues that basal-type carcinomas probably represent a subgroup of breast cancers in which the cancer cells are blocked at an early stage of differentiation.

We agree with Woodward and colleagues that the estrogen receptor is an important prognostic factor. Nonetheless, as shown in Table 3 of our article, the IGS is associated with the prognosis in estrogen-receptor–positive patients. Basal-cell breast cancers are generally estrogen-receptor–negative, so such tumors were removed from our analysis. Therefore, the prognostic power of the IGS is not simply based on the identification of estrogen-receptor–negative or basal-cell breast cancers. We also agree that the IGS was based on the isolation of breast-cancer stem cells from only a few samples and that analysis of a much larger group of patients could result in an improved signature. Nonetheless, the fact that a signature derived from just a few breast-cancer stem cells has prognostic power speaks to the value of investigating this population of cancer cells.

Dr. Wennmalm and colleagues ask whether the IGS has prognostic power if proliferation genes are removed. To test how important the proliferation-related genes are to the gene signature, we removed all 15 genes involved in cell proliferation or the cell cycle from the IGS and used the remaining genes as a signature for predicting the outcome of patients in the Netherlands Cancer Institute database. The remaining gene signature was still significantly associated with death (P<0.001; hazard ratio, 1.34) and metastasis (P<0.001; hazard ratio, 1.29).

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Lack of Association between Antimyelin Antibodies and Progression to Multiple Sclerosis

To the Editor: Seven different studies so far have shown controversial correlations (ranging from highly significant to not significant at all) regarding the predictive value of antimyelin antibodies in patients with a clinically isolated syndrome suggestive of multiple sclerosis.1-5 To validate our initial findings in other populations with a clinically isolated syndrome, we provided the same antimyelin-antibody immunoblot assay for all these studies. Controversial results may thus reflect differ-
We thank Reindl and Berger for their generous support in establishing the method, and we agree that our study’s failure to confirm their results is not due to technical differences. Serum antibodies against myelin oligodendrocyte glycoprotein and myelin basic protein had no prognostic value for progression to multiple sclerosis either in the total population or in subgroups analyzed in the Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study, whereas other factors with known prognostic relevance, such as the number of hyperintense lesions on T2-weighted MRI scans or of gadolinium-enhancing lesions on T1-weighted MRI scans or the presence of oligoclonal bands in cerebrospinal fluid, were confirmed. A potential effect of genetic variability may be further elucidated in the ongoing analysis of DNA and RNA expression in the BENEFIT study. We doubt that the longer mean interval between blood sampling and the initial event had a major effect on the results, because we did not find any increased association by comparing patients who had shorter intervals with those who had longer intervals.

We remain convinced that our study provided an ideal basis for a definitive validation of claims such as those raised by Berger et al.; it included a large number of patients from a representative sample of centers across Europe and Canada and was carefully monitored according to Good Clinical Practice standards. Patients were selected and observed according to predefined, independently evaluated and centrally reconfirmed inclusion and outcome criteria.

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igious beliefs, Curlin et al. (Feb. 8 issue) found that many physicians would refuse to tell patients about all legal treatment options in several critical situations. The authors advise patients to discuss these issues with their physicians in advance and change physicians if necessary.

It is unrealistic and unfair to expect patients to anticipate all conditions that may befall them, identify which ones might be problematic for their physicians, and agree either to reach a compromise or to seek care elsewhere. Medical visits are short and focused on current needs. Many people cannot change physicians. People encounter different physicians in different clinical situations.

The onus is on our profession to confront the willingness of so many of our colleagues to substitute their personal values for the fundamental right of their patients to know their treatment options.

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To the Editor: More disturbing than the data described by Curlin et al. is the authors’ conclusion: “ Patients who want information about and access to such procedures may need to inquire proactively to determine whether their physicians would accommodate such requests.” The authors suggest that patients have the obligation to know which procedures they might want or need and to query their physicians about whether they would provide or even discuss such procedures. The unspoken corollary is that if the physician says no, the patient is left to find a more responsive provider. To impose the philosophy of caveat emptor is morally inadequate, given the differences in power and class between many physicians and their patients. Physicians must not be permitted to disavow responsibility on the grounds of conscientious objection; rather, such practitioners must choose careers in which their fundamental values do not interfere with the autonomy and well-being of patients. Like conscientious objectors to military service, medical conscientious objectors must bear the consequences of their beliefs. A philosophy that permits physicians’ rights to trump their obligations to patients is unconscionable.

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To the Editor: Curlin et al. provide documentation that patients may not receive information about medical options because of the religious beliefs of their physicians. The history of Poland shows how a conscience clause can lead to the systemic deprivation of services. The Catholic Church’s significant influence in the post-socialist government, after 1989, led to the widespread use of the conscience clause, with de facto elimination of access to abortion, prenatal diagnosis, and most contraception. Four years later, the law actually criminalized abortion services, except in rare conditions, but abortion had already been made virtually inaccessible because of the use of the conscience clause.

Similarly, access to services is reduced in the United States with the mergers of nonsectarian and religious hospitals when religious restrictions are adopted by the merged entity. Survey research found that the scope of the care that doctors provide in such hospitals is significantly narrowed by the imposition of the conscience clause, especially limiting access to emergency contraception.

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TO THE EDITOR: The findings of Curlin et al. are timely for Chile, where there is a fierce controversy about whether the morning-after pill should be prescribed for girls as young as 14 years of age without their parents’ consent. The Chilean government, through a presidential decree, introduced the pill as a public health intervention. Opposition parties and the Catholic Church are against this new policy, stating that the pill is an abortion method and is illegal under Chilean law.
Those implementing this policy will certainly face difficulties. Physicians and pharmacists may object to the policy or even refuse to distribute the pill on moral or religious grounds. A health care system must establish clear criteria to allow the right balance between paternalism and the autonomy of patients in the case of medical issues that are controversial among health care professionals.

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To the Editor:
Curlin et al. note the association between physicians’ religiosity and their decreased willingness to refer patients for interventions that the physicians find morally objectionable, and the authors place this association within the context of paternalism versus patient autonomy. However, as physicians in the “high religiosity” category, we suggest an additional dimension. Paternalism and autonomy are principles based on rights: the right of physicians not to violate their own consciences and the right of patients to decide what to do. In counterpoise to rights are responsibilities. Because of our responsibility to our patients, we certainly cannot willfully harm them, but we also cannot assist them in harming themselves without failing our responsibility. If we truly believe that a given procedure violates patients’ intrinsic human dignity, then our responsibility to our patients mandates that we not help them procure that procedure. Thus, although our conscience is part of the picture, so too is our responsibility to our patients. Some circumstances do not allow us to assist in carrying out our patients’ desires without violating that responsibility.

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To the Editor: Until recently, I was an attending physician for patients with spinal cord injury during their initial rehabilitation. Many of those patients were on life support and despaired of going on with life, voicing a request for termination of their lives. Decisions based on patient autonomy alone would have had us doing so. Negotiations to “give life a try and wait at least a year before making any decisions” were successful and required frank discussion of the patients’ values as well as my own. Most of my patients did find value in their lives after such injuries.

The “moral compass” of a physician should not be ignored. Both patients’ autonomy and physicians’ values must play a role. Coercing physicians is no more defensible than coercing patients.

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The authors reply: If a judgment of conscience were merely a statement of personal preference or an expression of prejudice, the claims of Dr. Stotland and Drs. Ross and Clayton would be justified. But anyone who has been hounded by a sense that he or she has acted wrongly knows that is not how the conscience works. Those who act conscientiously do not “disavow responsibility” and “substitute their personal values for the fundamental rights of their patients.” Rather, they are engaging in the struggle to know and do the right thing and to understand and fulfill their moral obligations in a particular situation. This task cannot be externalized or delegated. Indeed, acting conscientiously is the heart of the ethical life, and to the extent that physicians give it up, they are no longer acting as moral agents.

Of course, the profession of medicine cannot permit all purported judgments of conscience. For example, the profession cannot permit physicians to refuse treatment of the sick on the basis of a patient’s ethnic background or sexual orientation. Such refusals undermine the primary goal of medicine, which is to restore the health of those who are sick. But the practices about which we surveyed physicians were not examples of treating sickness or restoring health. Unwanted pregnancy may have health risks associated with it, but it is not an illness. Terminal sedation is not the treatment of illness, unless the illness is consciousness itself. These practices are controversial precisely because there is disagreement about whether they are consistent with the goals of medicine.

With respect to controversial clinical practices, therefore, individual physicians should consider the moral arguments, take into account the particulars of each situation, and conscientiously determine the degree to which they can accommodate patients’ requests. If they cannot in good
conscience accommodate certain requests or help patients obtain certain legal procedures, they should, as a matter of respect, make that clear to patients at the earliest possible point. Ensuing discussions can enhance patient autonomy by allowing patients to make informed decisions about which doctor they want to entrust with their care.

Conscientious practice in a pluralistic world is messy even when peaceable. Yet the alternative is a society in which physicians are required to forfeit conscience in order to join the profession. Patients will not be well served by moral automatons who shape their practices, without struggle or reflection, to the desires of patients and the dictates of whatever regime is currently in power.

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Anchors Away

TO THE EDITOR: In the Clinical Problem-Solving case presented by Calfee et al. (Feb. 1 issue),¹ the discussant identifies a common heuristic error inherent in clinical problem-solving. In this case, the clinician’s reasoning became erroneously anchored to the nonspecific finding of granulomatous dermatitis provided by the pathologist on the basis of an initial skin biopsy. We agree that morphologic findings alone are not specific and should not be used as the single diagnostic tool for identification of idiopathic sarcoidosis. However, later in the discussion we are informed that the initial skin biopsy in fact showed a prominent lymphocytic infiltrate without frank granulomas.¹ We suspect that the pathologist was misled by another common heuristic error, the “clustering illusion” — that is, seeing a pattern, in this case granulomas, where none existed. It would be interesting to know whether the original skin-biopsy findings were consistent with lymphomatoid granulomatous, since the findings in the skin often mirror those in the lung.³ This case illustrates the importance of carefully reviewing with the pathologist “diagnostic” specimens in cases of idiopathic sarcoidosis, in particular when the course is atypical.

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TO THE EDITOR: In the case of a patient with lymphomatoid granulomatosis, the description in the text of an infiltrate composed of predominantly CD20+ B cells would be unusual for low-grade (grade I or II) lesions of lymphomatoid granulomatous. Such lesions typically are composed of few, large, angiocentric, CD20+, Epstein–Barr virus (EBV)—encoded RNA (EBER+) B cells against a background of numerous CD3+ T cells. Sheets of large B cells are seen in grade III lymphomatoid granulomatous, a variant of diffuse large-B-cell lymphoma.¹

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THE AUTHORS REPLY: Morgan and Berman appropriately highlight the importance of a careful review of pathological specimens with the pathologist (ideally face to face), particularly when the diagnosis is in question. In this case, a retrospective examination of the skin-biopsy specimen showed that it alone would not have provided the diagnosis of lymphomatoid granulomatosis. Knowing the final diagnosis obtained by lung biopsy,
the dermatopathologist later performed both CD20 staining (for B cells) and EBV in situ hybridization. The CD20 staining marked only rare cells, and the EBV hybridization was negative. Overall, the findings were consistent with an early stage of lymphomatoid granulomatosis or with sarcoidosis but diagnostic of neither.

Morgan and Berman also suggest that the pathologist may have fallen prey to the clustering illusion, a form of cognitive bias in which the human mind finds patterns where none exist or sees order in a random series. In this case, however, the pathologist did not describe granulomas but, rather, granulomatous inflammation, a broader term describing focal accumulations of activated macrophages with an “epithelioid” appearance. Post hoc review of the biopsy specimen confirmed that this interpretation was accurate. Thus, to our eye, the primary heuristic error was made by the clinicians in their interpretation of the biopsy report.

We agree with Allan’s comment about the pathological appearance of different grades of lymphomatoid granulomatosis. In this case, the lung-biopsy specimen was ultimately considered to show grade III lymphomatoid granulomatosis, in accordance with the description in the article and with the grading system described in the letter.

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TO THE EDITOR: In the Case Record of a patient with anemia and a low level of high-density lipoprotein (HDL) cholesterol, presented by Murali and colleagues (Dec. 28 issue), the discussant states that on rare occasions the presence of a paraprotein interferes with the measurement of HDL cholesterol, wrongly suggesting a low level. The discussant also states that the low levels of HDL cholesterol were due to genetic factors or were secondary to specific hormones, cigarette smoking, obesity, a low-fat diet, and drugs. Although all these secondary factors are found frequently, the most frequent cause of a low level of HDL cholesterol in hospitalized patients is simply an acute or chronic severe inflammatory disease with a marked acute-phase reaction. Like albumin and transferrin, HDL cholesterol drops and returns to normal within days after the end of the acute-phase reaction. Negative tests for acute-phase proteins are often overlooked as excellent markers of ongoing inflammation, and too often, a low albumin level is immediately regarded as evidence of malnutrition and a low HDL cholesterol level as evidence of a cardiovascular risk factor necessitating intervention. One should remember the complex changes that occur in lipoproteins during the acute-phase reaction in a patient with inflammation or infection.

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TO THE EDITOR: Murali and colleagues report on a patient with a paraproteinemia who was found to have an artifactually unmeasurable level of HDL cholesterol on a liquid-based HDL-cholesterol assay. Although the results were normal with the use of a non–liquid-based assay — presumably, involving the precipitation technique — they refer to a
case report suggesting that both kinds of assays may produce artifacts, since readings of very low HDL cholesterol levels were reported with the use of both methods in patients with paraproteinemia. Since an independent method such as ultracentrifugation was not used, it is possible that the case report they cite and others represent true HDL cholesterol deficiency associated with paraproteinemia, a phenomenon that Murali et al. do not consider in their discussion. In 2002, we reported on two patients with paraproteinemia and very low HDL cholesterol levels that were confirmed on the basis of ultracentrifugation, electrophoresis, and apolipoprotein A-I levels. We showed that immunoglobulin was bound to apolipoprotein A-I and that the immunoglobulin–HDL complexes were rapidly degraded by cultured macrophages (Fig. 1). Thus, the finding of a very low HDL cholesterol level in a patient with paraproteinemia may in some cases not be artifactual.

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THE DISCUSSANT REPLIES: Schifferli appropriately comments that acute or chronic inflammatory diseases, with a marked acute-phase response, can lower the level of HDL cholesterol. Our patient had no clinical or laboratory features of acute or chronic inflammation. However, Schifferli’s comment does reinforce the increasing awareness of lipid abnormalities in inflammatory processes.

Figure 2 in the Supplementary Appendix of this Case Record highlights the mechanism of falsely low levels of HDL cholesterol in liquid-based assays but not in solid-phase assays. Since the discrepancy was resolved in this Case Record, the need for ultracentrifugal studies, as suggested by Goldberg and Mendez, did not arise.

Figure 1. Binding of HDL to IgG in a Patient with Paraproteinemia but Not in a Control Subject.

Serum samples from a patient (P1 in our report) and a control subject were separated by agarose-gel electrophoresis, and the proteins were transferred to nitrocellulose and probed with specific antibodies against apolipoprotein A-I (Panel A) or antibody against IgG (anti-IgG) (Panel B). The migration of HDL was toward the anode, whereas the migration of IgG was cathodic. In the patient, but not in the control subject, the immunoreactivity to apolipoprotein A-I (arrowheads) occurs in the region of the gel to which the bulk of the IgG migrated. Panel C shows that incubation of 125I-labeled apolipoprotein A-I with increasing concentrations of purified IgG from the patient, but not from the control, in the presence of THP-1 macrophage cells resulted in a dose-dependant degradation of apolipoprotein A-I by IgG from the patient but not from the control. The results are shown as the mean (±SD) value for triplicate incubations, expressed as micrograms of apolipoprotein A-I degraded per milligram of cell protein over a period of 6 hours.

A Anti-Apolipoprotein A-I
B Anti-IgG
C 125I-Labeled Apolipoprotein Degradation

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In contrast to the patients described by Mendez and colleagues, who had IgG monoclonal gammopathy and low levels of HDL cholesterol, our patient had IgM monoclonal gammopathy. Since macrophages have receptors for the Fc portion of IgG but not for IgM, enhanced catabolism of apolipoprotein-A-I–IgG complexes by macrophages does not explain the low HDL cholesterol levels in our patient. In fact, Goldberg reinforces our observation that when confronted with unexplained low levels of HDL cholesterol, clinicians and clinical pathologists need to rule out a paraproteinemia, using appropriate laboratory methods to ensure that the observed low HDL cholesterol levels are not due to paraprotein-associated interactions or interference in assay systems.

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Alendronate and Atrial Fibrillation

TO THE EDITOR: In this issue of the Journal, Black et al. report on a significant increase in the risk of serious atrial-fibrillation adverse events (defined as events resulting in hospitalization or disability or judged to be life-threatening) associated with once-yearly infusions of intravenous zoledronic acid for the treatment of osteoporosis in postmenopausal women. However, there was no increased risk of all adverse events of atrial fibrillation with such infusions.

We reviewed the results of the Fracture Intervention Trial (FIT), a randomized study of alendronate sponsored by Merck, which involved 6459 postmenopausal women (mean age, 69 years). The University of California at San Francisco coordinating center collected the data, created the data set, and provided reports to the data and safety monitoring board. At the board's request, a physician at the coordinating center who was unaware of study-group assignments confirmed potential atrial-fibrillation adverse events. The final 1997 analysis that was reported to the Food and Drug Administration showed 47 serious atrial-fibrillation adverse events (1.5%) among patients receiving alendronate versus 31 (1.0%) among those receiving placebo during an average of 4 years (relative hazard, 1.51; 95% confidence interval [CI], 0.97 to 2.40; P = 0.07) (Fig. 1). There was no increased risk of all atrial-fibrillation adverse events: 81 events (2.5%) versus 71 events (2.2%) (relative hazard, 1.14; 95% CI, 0.83 to 1.57; P = 0.42). At that time, a true association between atrial fibrillation and the administration of alendronate was considered to be very unlikely in view of numerous comparisons of potential adverse events, no association for all atrial-fibrillation adverse events, and no apparent biologic plausibility.

The trend toward an increased risk of serious but not atrial-fibrillation adverse events in the FIT trial resembles the pattern observed in the study of zoledronic acid by Black et al. How potent bisphosphonates might increase the risk of serious atrial fibrillation is unclear. However, parenteral administration of bisphosphonates stimulates the release of inflammatory cytokines, and increased levels of inflammatory cytokines have been associated with an increased risk of atrial fibrillation. It is not known whether oral bisphosphonates also increase cytokine levels. Shifts of calcium within atrial cells can predispose patients to atrial fibrillation. Potent bisphosphonates cause a very small decrease in serum calcium levels, but the relevance of this finding to atrial electrophysiology is uncertain. Explanations...
must account for an increased risk of only serious atrial fibrillation.

The possibility of an increased risk of atrial fibrillation should be examined in other studies of bisphosphonates and assessed in trials of potent inhibitors of bone resorption. This potential risk must be weighed against the reduction in fracture risk.

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Dr. Cummings reports receiving consulting and advisory-board fees from Amgen and Organon, lecture fees from Merck and Lilly, and grant support from Amgen, Novartis, Lilly, and Pfizer. Dr. Black reports receiving grant support and honoraria from Novartis and Merck. No other potential conflict of interest relevant to this letter was reported.


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GERD: REFLUX TO ESOPHAGEAL ADENOCARCINOMA


Esophageal cancer is the seventh leading cause of all deaths from cancer worldwide, with an estimated 14,000 deaths from this cancer in the United States alone in 2006. Since the 1970s, esophageal adenocarcinoma has been the neoplasm with the fastest-growing incidence of any cancer in the Western world. This rising incidence implies a need for improvement in identifying those at risk for the disease and in both intervention and prevention. Regrettably, there is a lack of consensus among experts regarding the diagnosis and management of Barrett's esophagus. A book that is focused on this important subject has been long overdue.

This timely and authoritative book was written by two masters in the field whose experience spans two decades and includes supervision of studies involving more than 10,000 patients. The book is well written and demonstrates the advantages of having a limited number of authors and a narrow focus — namely, consistency of style and a cohesive philosophy. There is structural coherence, with a logical progression of the 17 chapters and minimal overlap between them. Early chapters provide overviews of gastroesophageal reflux disease (GERD) and Barrett's esophagus, followed by a review of embryological development of the upper gastrointestinal tract and of normal anatomy and histology. Subsequent chapters document the pathology of GERD at the cellular and anatomic level, with evolution through Barrett's metaplasia to adenocarcinoma. The book ends with suggestions for research strategies, discussions of the rationale for management of GERD and Barrett's esophagus, and strategies for preventing reflux-induced adenocarcinoma.

The book is compelling reading, made more so by its historical approach, as the authors trace the gradual evolution of medical thought in the field. A further strength is the literature review at the end of each chapter, where the authors summarize and offer their often strong opinions of landmark studies in the field.

The authors believe that the increasing incidence of esophageal cancer is at least partly a consequence of a failed medical approach to the precursor conditions of GERD and Barrett's esophagus. This problem, they write, stems from fundamentally flawed definitions of both conditions that underestimate their true prevalence, as do current practice guidelines stating that there is no need for biopsy of endoscopically normal gastroesophageal junctions. The authors argue that esophageal adenocarcinoma is preventable and that recognition of earlier stages in the reflux-to-adenocarcinoma sequence would allow for interventions that might heavily influence its incidence. They also contend that the current therapeutic approach to GERD — acid-suppressive therapy — might be promoting the development of adenocarcinoma and that GERD should be managed with antireflux surgery.

The authors therefore propose several radical changes in the field, including new criteria for defining the gastroesophageal junction, GERD, and Barrett's esophagus, as well as a new classification system for adenocarcinoma of this region. They recommend a new biopsy protocol for patients with GERD who are undergoing endoscopy. They call for a radical overhaul in our current thinking and urge that GERD be viewed as a premalignant condition and treated with an appropriately aggressive approach.

Criticisms of this book are minimal. Several illustrations are faint and sometimes blurred, appearing to be scanned or photographed images that have not reproduced well. The authors are very opinionated, and many readers will not agree with their views, several of which are controversial. Although many of their ideas are indeed provocative and deviate from current consensus, we feel that the authors’ vast experience gives their opinions importance — their perspective must be carefully considered. We therefore feel that this book is es-
sential reading for anyone with an interest in esophageal disease, and particularly in GERD and esophageal adenocarcinoma.

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CHALLENGES IN INFLAMMATORY BOWEL DISEASE


INFLAMMATORY BOWEL DISEASE AND FAMILIAL ADENOMATOUS POLYPOSIS: CLINICAL MANAGEMENT AND PATIENTS’ QUALITY OF LIFE


It was not the intention of the editors and authors of Challenges in Inflammatory Bowel Disease to produce yet another comprehensive book on inflammatory bowel disease, but instead to consider specific issues. The book’s chapters are divided into five major sections: “Clues to Etiology and Pathogenesis,” “Diagnosis and Assessment,” “Management of Ulcerative Colitis,” “Management of Crohn’s Disease,” and “Special Management Problems.”

Have the authors succeeded in their ambitious aims? On balance, the answer is a qualified yes. Indeed, many of the chapters — all written by recognized experts in their fields — contain important information. I particularly liked the chapters on microbial sensing, the role of appendectomy, and the management of refractory distal colitis. But the book also has substantial weaknesses. Only a few practical algorithms are provided. The illustrations are limited and in black and white. Most of the references are from 2004 or earlier, and a lot has happened in the field since then. There are some referencing errors as well as occasional overstatements — such as that the role of the Paneth cell provides a convincing explanation for the preponderance of Crohn’s disease in the terminal ileum.

In my view, this book cannot be recommended for the general gastroenterologist or digestive surgeon because it lacks essential components. It will, however, be useful for trainees or specialists with an interest in inflammatory bowel disease or for scientists who want expert information on topics outside their own area. The editorial team is made up of world leaders in the study of inflammatory bowel disease, and the basic and clinical scientific information they present is of high quality.

Another book on a similar topic, Inflammatory Bowel Disease and Familial Adenomatous Polyposis, deals with the two diseases in its title, and there is an emphasis on surgery throughout the book that is not mentioned in the title or subtitle. Perhaps the theme of colorectal disease and surgery is the justification for linking the two diseases in one textbook. The foreword describes the book’s three objectives: to review current methods of treatment, to discuss management of complications associated with these therapies, and to give an account of new therapies. The chapters are divided into four sections.

The authors of the first section cover the role of magnetic resonance imaging. The second section is a discussion of inflammatory bowel disease and includes chapters on epidemiology, pathology, dysplasia, motility, extraintestinal and perianal manifestations, endoscopy, nutrition, quality of life, pregnancy and urogenital problems, therapies and various aspects of surgery, and bowel and liver transplantation.

The authors of the articles in the third section cover polyposis, including genetics, extracolonic manifestations, desmoid tumors, and various aspects of conventional and laparoscopic approaches. The description of the laparoscopic approach to familial adenomatous polyposis is detailed and
well illustrated. Articles in the fourth section provide information on the psychological aspects of colitis, the interdisciplinary aspects of the management of inflammatory bowel disease and familial adenomatous polyposis, the role of ileal pouching in indeterminate colitis, the surgical management of emergencies, and rehabilitation.

This book reflects the authors' diagnostic and therapeutic expertise. Discussions are up to date, and current topics are well referenced. However, there is excessive redundancy. Despite the number of appropriate algorithms that are included, this book does not feature enough pathophysiology or basic science to justify recommending it to gastroenterologists. The strength of the book is surgical technique and outcome, and for this reason I recommend it for surgeons in training and in clinical practice — but readers will have to search for the surgical “pearls.”

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SLEEP APNEA: CURRENT DIAGNOSIS AND TREATMENT
(Progress in Respiratory Research. Vol. 35.)

The rapid growth of sleep-disorder medicine as a subspecialty, and with it the growing number of patients in all medical settings who have received diagnoses of sleep disorders, has created the need for reference works accessible to the clinician seeking a focused and succinct introduction to the field. This is particularly true for the sleep apnea syndromes, as those are arguably the sleep disorder diagnoses having the largest effect on the rest of medicine. In addition, the recent inclusion of training in sleep-disorder medicine as a formal requirement of fellowship programs in pulmonary and critical-care medicine has highlighted a serious deficit in didactic texts that include both basic clinical science and pragmatic clinical guidelines.

Sleep-disorder medicine already has its share of “definitive” texts. At more than 1000 pages in length, however, these books represent a serious commitment for physicians with looming board exams and students with a still-fledgling interest in the subject. In addition, these books are necessarily broad in scope, covering all of sleep medicine — from common disorders to rare ones — thereby limiting depth in any one area. Enter Sleep Apnea, a slender book (just shy of 250 pages) that is part of the Progress in Respiratory Research series from Karger. Its modest heft makes it a reasonable addition to a briefcase or backpack. Despite the easy lifting, however, this book aspires to provide a comprehensive introduction to sleep apnea syndromes, with chapters covering everything from basic sleep physiology to the clinical features of sleep-disordered breathing in pregnancy.

Although the book falls short of its promise in a number of ways, there is still much to recommend, and I have already found this book to be a valuable resource in the clinic, in the laboratory, and in the classroom. The chapters on the physiology of breathing during sleep and the clinical presentation of obstructive sleep apnea are particularly good — pitched perfectly for students and residents who do not have extensive pulmonary training. The last several chapters, covering sleep apnea syndromes in special populations (such as children, the elderly, and pregnant women), are valuable as well. Although problematically terse in places, these chapters provide clinicians with an accessible introduction to these important overlapping areas. For example, the chapter on sleep-related breathing disorders in children includes a beautifully brief summary of the clinical approach to a child with sleep apnea and the factors that should be weighed in considering surgical treatment.

The identified need, however, was for a book that could serve in the classroom, in the fellowship program, or on the reference shelf of the non-specialist. Against this measure, the book falls short. The problems lie in several key areas. First, several chapters are already out-of-date. Although it is true that the gestation period for a book of this kind is an inherent barrier to currency, there are a few chapters that are so dated or incomplete that students should be advised against reading them. It is difficult to imagine, for example, that a chapter titled “Physiology of Sleep and Dreaming” written in the past 6 years could omit mention of the ventrolateral preoptic nucleus of the hypothalamus. First described in 1996, by 2001 it was understood for its preeminent role in the control of sleep, but the anatomy and physiology of this structure escape mention in the chapter.
A look at the references hints that the problem with this crucial chapter may be less currency than focus — there are current references on the modeling of sleep-wake regulation, for example. As it stands, however, this is not a useful introduction to the neurobiology of sleep for those new to the field. The problems with the chapter on the genetics of sleep apnea are more understandable, given the focus of recent research on this topic. The authors of this chapter concentrate on a review of the genes that may be involved in the development of obesity or variations in craniofacial structure, an approach that has not been particularly productive in understanding the pathophysiology of sleep apnea. Promising findings from more empirical, population-based studies have appeared only within the past few years.

The other major disappointment lies in the selection of chapter topics. The preparation of a collaborative book such as this one always requires compromises between the ideal table of contents and the authors who are available (and willing) to write. Here, the tension between the two may be the explanation for some perplexing choices. Continuous positive airway pressure (CPAP), the treatment of choice for most patients with obstructive sleep apnea, is covered thoroughly in chapters dealing with both theory and practice. Alternative therapies are addressed in a series of much shorter chapters that include two extremely brief discussions of cardiac pacemaker therapy and electrical upper-airway muscle stimulation (surgical revision procedures, which have yielded some impressive results, are not covered). Another chapter is devoted to pharmacology and behavior modification. A single chapter dealing with alternative approaches, in which the strengths and weaknesses of each could be contrasted and the selection criteria reviewed, would have been far more valuable to the clinician. Almost as frustrating is the inclusion of an entire chapter on humidification in CPAP therapy but only a few paragraphs on the broader clinical problem of ensuring patients’ compliance with this problematic but effective therapy. Other chapters seem to belong on the editorial page with this problematic but effective therapy. Other chapters seem to belong on the editorial page rather than in a teaching resource. One hopes the authors of the chapter “Oxidative Stress — The Culprit of Obstructive Sleep Apnea Syndrome” do not come to regret the omission of a question mark from its title by the time the next edition of the book is due.

So, still lacking a book I can recommend without reservation to students, residents, and colleagues newly interested in sleep, I slipped this book into a very narrow space on my bookshelf, realizing that sometimes slender is just another word for thin.

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CORRECTIONS

Anchors Away (February 1, 2007;356:504-9). The legend for Figure 5 (page 508) should have read “Panel B is a higher-power view showing nuclear staining of abnormal lymphocytes (arrow) for Epstein–Barr virus—encoded RNA (Epstein–Barr virus in situ hybridization),” rather than “for Epstein–Barr virus DNA (Epstein–Barr virus in situ stain).” The text has been corrected on the Journal’s Web site at www.nejm.org.


NOTICES

Corrections

For letters to the Editor: authors.nejm.org
For information about the status of a submitted manuscript: authors.nejm.org
To submit a meeting notice: meetingnotices@nejm.org
The Journal’s Web pages: www.nejm.org
A 68-year-old man with hypertension presented with vague abdominal pain. Ultrasonography of the abdomen showed a renal mass in the left kidney. A computed tomographic scan of the abdomen showed a mass consistent with a renal-cell carcinoma in the upper pole of the left kidney (arrowhead) and a duplication of the inferior vena cava (arrow). The aorta, which has calcifications, can be seen between the duplicate inferior vena cavae. The inferior vena cava is formed between weeks 6 and 10 of gestation. Duplication occurs in 0.2 to 3.0% of the general population. The infrarenal portion of the inferior vena cava is formed from the right supracardinal vein while the left supracardinal vein regresses. A duplicate inferior vena cava results from persistence of both the right and left supracardinal veins. Although such anomalies are generally asymptomatic, they have important clinical ramifications in certain settings (e.g., when pulmonary embolism occurs after filter placement in the right inferior vena cava because of the presence of a left inferior vena cava). They can also be a source of diagnostic uncertainty and make surgery more hazardous. Knowledge of caval anomalies can prevent misinterpretation of mediastinal masses, iliac occlusion with venous collaterals, and paravertebral lymph-node enlargement. In this patient, a complete resection of the renal-cell carcinoma, which was confined to the kidney, was successful.

Transcript

Rachel Gotbaum: I’m Rachel Gotbaum with the New England Journal of Medicine. On Wednesday, April 11th, the U.S. Senate passed a bill that would loosen restrictions on federal funding of stem-cell research. I’m speaking with Senator Orrin Hatch of Utah. He was one of numerous Republicans who supported this bill.

You’re a pro-life Republican.

Orrin Hatch: That’s right.

RG: You come from a politically conservative state. How did you come to support stem-cell research. What happened?

OH: Well, I have to admit that it was a very, very difficult process for me because I met with religious leaders on both sides of the abortion issue. I met with ethicists on both sides. I met with scientists on both sides, doctors on both sides, political people on both sides. I have to tell you I really believe that it was absolutely correct for me to support embryonic stem-cell research, and I believe that being pro-life is more than just caring for the unborn — it’s caring for the living as well. And this type of research is the most promising research in the history of the planet, and it ought to be followed through, and it ought to be followed through with the highest moral and ethical standards that we can possibly come up with. And the way to do that is to have NIH fully involved.

RG: Did something happen? Did a case come up? What was the turning point?

OH: Well, there was a case. I can’t say that it was the only reason why my mind was changed, but there was a little Utah boy — he was 4 years of age — who was brought to me. His name was Cody Anderson. He was 4 years of age, and you can imagine the horror his family had when they found out that he had exactly the same virulent diabetic condition that his grandfather had, who died at the premature age of 47 due to complications of diabetes after a series of something like 27 painful and debilitating and ultimately unsuccessful operations. I can still remember that little exhausted boy falling peacefully asleep in his father’s arms in my office as his family visited me in support of more funding for diabetes research. It dawned on me that we owe the best we can to these kids.
What if we could find a treatment and/or cure for virulent juvenile diabetes or for diabetes in general? That would save us trillions of dollars in health care costs over the years, plus a lot of lives, and give people a better quality of life who suffer from these type of problems. And I’d say that was part of the reason, certainly.

And then I met with a series of Nobel laureates. And I’m aware of some 40 Nobel laureates who share this view on the potential of embryonic stem-cell research. I met with a number of the leading scientists, and they all conveyed an urgent sense that this new avenue of science is very, very important, and worth the effort to address the — you know — the attendant policy, ethical, and political challenges.

**RG:** How did you move through the ethical issues as a pro-life, anti-abortion person yourself?

**OH:** Well, for the life of me, I cannot understand how anybody can argue that we should destroy 7000 to — or cast aside — 7000 to 20,000 in vitro fertilized eggs a year as hospital waste and thus kill them, and that that is a pro-life position. And not use them for the benefit of mankind. Especially little boys like Cody Anderson, or any number of other people throughout our society. With federal government help from NIH and a proper administration, we may be able to solve many of the health care problems of mankind and at the same time save trillions of dollars while doing ethical research.

**RG:** Have you met with President Bush and discussed your views and heard his views on this?

**OH:** Well, he knows my views, and I know how sincere he is. Now I told the White House after the first time that we passed the embryonic stem-cell research bill that look, if you’re concerned about the destruction of the embryo — the so-called, quote — destruction — unquote, of the embryo — if you’re so concerned about that, then we have about 300 to 400 existing new embryonic stem-cell lines created by the private sector. Why don’t you let NIH partner with those private-sector companies that are willing to partner with them in the development of those existing embryonic stem-cell lines, because that way you would not have had the government participate in this so-called, quote — destruction — unquote. But of course, the answer was, well, that would be encouraging more stem-cell lines to be done and the destruction of human life.

But I really don’t believe that the President has been given good advice on this. I believe the advice he has been given is political and not scientific. And I don’t believe he has had the time to really study it as I have, as someone who has helped leading the fight up here. But — let’s be honest about it — he believes that they’ve taken a principled position. And from their viewpoint, they have.

**RG:** The President has promised to veto this bill.

**OH:** Well, he will.

**RG:** Are there any prospects for an override, in your view?
OH: Well, I think we were one vote away. Now I have to, I have to chat politically for a minute. I begged my Democrat colleagues to not politicize this issue in the last election. They did. They just couldn’t help themselves. I said I know of at least one vote that resented the politicization of the issue that we probably would have had, which would have given us 67 votes. And I believe there may have been others who just got resentful when they saw the politicization of it.

Look, it’s no secret, Michael J. Fox went up and down the land for a variety of Democratic candidates making this an issue. Now, I happen to like Michael J. Fox. I understand his anxiety about this with the malady that he has — the Parkinson’s disease that he has. And I think he meant to be bipartisan, but in the process, I think helped to defeat a man who would have been with us, and that’s Jim Talent of Missouri. I think I could have gotten to Jim Talent. I was talking to him all the time, and he was very concerned about it. But at that point in the election process pretty well had to stand with his prior conviction, but he was open to it. I think we had a reasonable chance to get him. But not just Jim Talent. There were some others, too, and then there — I’ve had some people come to me and say I wish they hadn’t politicized this, I don’t think I can vote for it now.

RG: Let’s talk a little bit about therapeutic cloning. You’re a supporter of therapeutic cloning. Where are we with this bill that you’ve coauthored with Senator Dianne Feinstein of California?

OH: Well, that bill doesn’t have a chance right now. I think if we actually did the in vitro fertilization bill that would allow those cells to be used — rather than cast aside and killed — but used for research to help current suffering people, and if that research does go forward and becomes effective research, then I think there will be a hue and a cry to do the regenerative medicine research that we’ve been talking about — some call it therapeutic cloning. But I think we’re a far cry from being able to get that type of bill through.

RG: So what is the outlook, given the momentum of this stem-cell research initiative? What will it take to make it law, in your view?

OH: Well, we’re going to win. I mean, we’re gradually just making the case, but unfortunately we’re 7 years behind where we would be in research had we not had this failure to win. It’s going to probably take another Congress to be able to really win on this issue.

RG: Orrin Hatch is a Republican senator from Utah.