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**Pentothal Postcards**
The Population Council submitted a new drug application to the Food and Drug Administration (FDA) on March 14, 1996, for the progesterone antagonist mifepristone (also known as RU 486) to be used as an abortifacient. The application was based on two studies, involving a total of 4600 women, of the drug’s safety and efficacy in the termination of early pregnancies. Four years later, a review article in the Journal cited 14 studies of mifepristone with more than 300 patients per study and a total of 26,000 treated women. By the summer of 2000, mifepristone had been used to treat more than 500,000 women in nearly a dozen countries in which it had been licensed. The FDA approved the drug for use in the United States on September 28, 2000, after more than 80 supplemental filings and submissions by the sponsor in response to queries from the agency. Mifepristone was one of 18 new molecular entities approved by the agency that year. Its 54-month approval time contrasted with the median total approval time of 15.6 months for all new molecular entities approved that year.

That original approval included a “black-box” warning that use of the drug could result in incomplete abortion requiring surgical intervention. It advised prescribers to be sure that appropriate provisions were made to provide that care when needed. On November 15, 2004, the FDA strengthened the warning in the black-box labeling of mifepristone to call attention to potentially fatal complications (ruptured ectopic pregnancy and septic shock) associated with its use in terminating early pregnancies. At the same time, the agency updated its Web site (http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm) to reflect the deaths of three U.S. women who had taken the drug since its introduction in the United States; one of these deaths was due to a ruptured ectopic pregnancy, and two were due to septic shock. This updating occurred during the same week that FDA officials were called before a congressional committee investigating the high-profile withdrawal of rofecoxib (Vioxx) in order to respond to charges of lax oversight of the drug industry. Some used the circumstances to call for the withdrawal of mifepristone on the grounds that it, too, posed an undue safety risk.

On July 19, 2005, the agency reported that it was aware of four U.S. deaths due to sepsis in women who had used mifepristone and announced its second revision to the black-box warning in eight months. This revision named Clostridium sordellii as responsible for
two of the deaths and specifically called attention to the somewhat unusual and rather distinctive signs and symptoms associated with these infections — an absence of fever but the presence of refractory hypotension, hemoconcentration, effusions in multiple serous cavities, and dramatic leukocytosis. A Canadian woman is also known to have died in 2001 of the same bacterial infection under similar circumstances.

These deaths have important implications both for the care of individual patients and for public policy. Disturbing aspects of the cases described by Fischer et al. in this issue of the Journal (pages 2352–2360) include the following: all the women were young and healthy; they had apparently successful procedures (there was no evidence on autopsy of retained products of conception); their clinical presentations were somewhat cryptic because they had cramping, which is very common after the procedure, and no fever; and they all died remarkably rapidly after presentation. The efforts of the FDA and the Centers for Disease Control and Prevention to post information about these deaths on their Web sites, a “Dear Health Care Provider” letter from the manufacturer, publication of a “Dispatch” in the Morbidity and Mortality Weekly Report,2 and the article by Fischer et al. will all help to alert clinical care providers to this potentially lethal syndrome.

Inevitably, the public health question of the safety of this method of pregnancy termination must be addressed. Some critical questions are: How great is the risk? With what is it appropriate to compare this risk? And what are the alternatives?

The manufacturer reports that “more than 460,000” procedures have been performed in the United States since the drug’s approval. There is some uncertainty about this number because, although the manufacturer knows how many tablets it has shipped, it is not absolutely certain how many procedures have been performed with those tablets. The FDA-approved dose per procedure is three 200-mg tablets (600 mg total), and the tablets are packaged three to a pack. But on the basis of substantial evidence of equivalent safety and efficacy, the World Health Organization has recommended a dose of 200 mg per procedure. Most providers, including large institutional providers such as Planned Parenthood of America, routinely use the 200-mg dose. The manufacturer’s estimate of 460,000 procedures is based on the assumption that most entail use of the lower dose. These figures would suggest that the risk of death from infection is less than 1 per 100,000. In the United States, the risk of death from any cause associated with attempting to carry a pregnancy to term is 8 to 10 times that.

The more appropriate comparison, however, is with the risk associated with other methods of inducing abortion. The overall maternal mortality rate associated with induced abortion in the United States is approximately 1 per 100,000. That overall rate is a “blended” rate including all the procedures performed in the United States at all gestational ages. The gestational-age–specific rate increases exponentially from 0.1 per 100,000 at 8 weeks’ gestation to 8.9 per 100,000 at 21 or more weeks’ gestation. Mifepristone is approved for the termination of pregnancies at less than seven weeks’ gestation. Therefore, the appropriate comparison is with a risk of 0.1 per 100,000 for surgical abortions performed at less than eight weeks’ gestation.

As tragic as the deaths of these young, healthy women are, they remain a small number of rare events without a clear pathophysiologic link to the method of termination. Patients should be informed of this risk before they consent to the procedure and should be vigilant for symptoms after the procedure. Providers must be aware of this potential complication and not be reassured by the absence of fever. Regulators should keep this rare complication in perspective and not overreact to scant data by prematurely foreclosing the only approved medical option for pregnancy termination. It may be difficult, however, to maintain equipoise on this issue in the wake of recent perceived regulatory lapses and amid the turbulence created by any discussion about abortion.

An interview with Dr. Greene can be heard at www.nejm.org.
Observational Studies of Drugs and Mortality
Wayne A. Ray, Ph.D.

Randomized controlled trials of therapies for the primary and secondary prevention of cardiovascular disease increasingly are powered to study overall mortality. The interventions frequently treat asymptomatic risk factors among high-risk patients and have a diverse spectrum of potential adverse effects. Thus, medications such as clofibrate or encainide that successfully alter surrogate endpoints but increase the rate of death are of little clinical interest. Many believe that a new preventive therapy for cardiovascular disease should be used sparingly, if at all, until clinical trials establish equivalence or even superiority to existing treatments in terms of mortality from all causes.

When randomized, controlled trials, for a variety of reasons, fail to provide data on overall mortality, should epidemiologic studies step into the breach? An observational post-marketing study by Wang et al. in this issue of the Journal (pages 2335–2341) compares conventional and atypical antipsychotic medications and shows that the former are associated with a 37 percent increased risk of death. Such data on mortality from all causes will be of keen interest to patients and their physicians. However, there are formidable challenges involved in conducting studies of mortality that are clinically relevant and scientifically accurate.

A finding of an increased rate of death from any cause is always important. However, those who design and fund studies should consider whether negative results would be of similar scientific interest. That is, is death from any cause plausibly a sensitive indicator of the risks and benefits associated with a given medication? Mortality is always pertinent with regard to medications (such as lipid-lowering agents) used to treat asymptomatic patients, because the only benefit is prevention of future disease. For medications that have a broad spectrum of potentially serious side effects or that are used to treat patients at high risk of disease, overall mortality is an excellent integrated measure of overall benefit in comparison with risk.

However, an exclusive focus on mortality may obscure important effects of medication, particularly when study findings are negative. For example, in the treatment of gastroesophageal reflux disease with proton-pump inhibitors, it probably would make little sense to base decisions about therapy and policy on negative results with regard to overall mortality in studies comparing these inhibitors with antacids. Among typical patients, the baseline mortality risk would be too low to provide adequate power, and even in high-risk populations, the further loss of power and potential bias introduced by deaths unaffected by these drugs would conceal medication effects. Furthermore, an analysis of overall mortality may contribute little to the elucidation of a biologic basis for a given drug effect. Recognizing that overall mortality often does not tell the full story, the investigators involved in individual clinical trials almost always report other primary end points.

In a randomized, controlled trial, study treatments are initiated at or after the beginning of follow-up. This approach has two important advantages. First, it ensures the identification of adverse events that occur early in therapy, which is often a period of increased risk. For example, in comparisons of medical and surgical therapies, follow-up is begun before surgery to account for perioperative events. Second, prognostic factors can be measured before they are influenced by the treatments. Observational studies can emulate this characteristic of randomized, controlled trials with the inclusion of new user designs, which synchronize the beginning of follow-up with the start of drug use.

Like randomized, controlled trials that study mortality, observational studies usually require very large sample sizes. Thus, most post-marketing studies use data that are already available, such as those that are obtained from automated administrative databases or those from multipurpose studies. Among the minimum requirements for the use of such databases are a defined population for which entries and exits are tracked, information about the occurrence and date of death (and, ideally, the cause), data regarding potential prognostic factors (i.e., confounders) that may differ among the study groups, and ongoing quality control and validation of crucial elements of the data.

The database must include information that permits the tracking of drug use on a day-by-day basis. The capacity to define the
point at which medication use begins is essential. Many drug effects can occur only when the patient is using the drug, and thus both the database and the analysis must account for medication exposure that changes with time. For this reason, cohort studies that collect information on an annual basis (or even less frequently) often are not suitable for post-marketing studies. For case-control studies, which are often recommended for rare events, obtaining accurate, unbiased information about medication used by persons who have since died and by those in comparable control groups is challenging.

Controlling for confounding variables is particularly difficult in studies involving overall mortality. Effects of medication on overall death rates may be small, because most drugs are unlikely to affect all causes of death equally. For example, coxibs may increase the risk of death from cardiovascular causes but decrease the risk associated with colorectal cancer. Yet it is precisely in the study of small effects that the influence of confounding is most difficult to rule out.

Illnesses that precede death may alter drug use and introduce confounding. For example, patients with life-threatening diseases often receive hypnotic therapy, which could lead to a non-causal positive association of such treatments with overall mortality. Conversely, the use of nonsteroidal antiinflammatory drugs may be avoided in patients with serious illnesses, leading to a negative association.

To avoid this confounding, one might consider emulating the intention-to-treat analysis of a randomized, controlled trial. Follow-up would begin at a defined point in the patient’s clinical course, and drug exposure would be determined at this time and remain fixed throughout follow-up. However, unlike randomized, controlled trials, observational studies provide no incentives for patients to continue initial therapy. Fixed-exposure studies thus are likely to have substantial misclassification of data regarding exposure, as patients stop and start medications. This misclassification will obscure the true effects of medication and exaggerate the relative effect of residual confounding by baseline differences, such as drug indication and related factors, between drug users and nonusers.

A serious error in fixed-exposure studies is the determination of drug exposure after follow-up has begun. For example, some investigations of the effects on mortality of inhaled corticosteroids among patients with chronic obstructive pulmonary disease initiated follow-up at the time of hospital discharge but classified patients as drug users if they started therapy at any time in the subsequent 90 days. As Suissa notes, this approach gives drug users “immortal” person-time (i.e., from hospital discharge to start of drug) and thus substantially overestimates the beneficial effects of corticosteroids on the rate of death.

Death is affected by both the occurrence of disease and the patient’s capacity to withstand the consequences of disease. The latter is influenced by a host of factors that are potentially difficult to measure. For example, the care given to patients who receive new medications may be better (or worse) than that for patients who receive older therapy, and this may affect mortality. The potential influence of these factors is illustrated by an analysis of data from trials in patients with cardiovascular disease demonstrating that among patients assigned to placebo, death rates are lower among those who adhere to therapy. Many believe that this “healthy drug user” effect accounts for at least some of the discrepancies between randomized and nonrandomized studies involving hormone-replacement therapy and vitamin supplements.

Studies comparing drugs that have similar indications may provide the best defense against confounding. However, even in such a case, patients will be assigned to therapies for reasons that are difficult to measure (“channeling”). The meticulous measurement of all factors plausibly related to prognosis is essential. One of the criteria for causality in epidemiologic studies is specificity of effect, because a change of similar magnitude in multiple end points is consistent with channeling and other biases. When possible, the study of individual causes of death or other, more specific end points is desirable.

The relative effectiveness and long-term safety, including effects on mortality, of many widely used medications are poorly understood. Randomized trials would provide the most reliable data; however, in the absence of material reform of the system for the approval of new drugs, there is little incentive to conduct such trials. Nonrandomized studies can provide valuable information, as does the thoughtful study by Wang and colleagues. However, observational studies of overall mortality are particularly susceptible to numerous biases and thus must be conducted with extreme care.
Politically Correct Human Embryonic Stem Cells?

Davor Solter, M.D., Ph.D.

Human embryonic stem cells are currently viewed as a very promising basis for regenerative medicine of the future. However, to be eligible for federal funding in the United States, researchers must work with federally approved human embryonic stem-cell lines — that is, the few lines derived before August 2001. There is a concerted effort and hope among scientists and legislators that federal funding could be extended to cover as yet nonexistent embryonic stem-cell lines if such lines could be derived without destroying a viable human embryo. The authors of two recent studies1,2 have suggested that such lines can be derived either from one cell of a cleaving embryo, leaving the remaining embryo to develop normally, or from an “embryo” that is rendered genetically incapable of normal development.

Chung et al.1 derived mouse embryonic stem-cell lines from single blastomeres of embryos at the eight-cell stage and transferred the remaining seven-cell embryos into surrogate mothers, in which they developed into normal mice. They argue that the same procedure (single-blastomere biopsy) could be applied to human embryos obtained by in vitro fertilization (IVF), thus allowing the derivation of an embryonic stem-cell line concomitant with the normal development of the embryo from which the cell line originated (see Figure 1).

Though theoretically possible, the procedure poses considerable problems that make its use unlikely in humans. Infertile couples resorting to IVF are unlikely to accept the additional risk imposed by both embryo biopsy (reduced probability of success) and the probable need to freeze the embryo while the embryonic stem cells are being obtained. It has been argued that the additional risk to the embryo will be balanced by the benefit of having genetically compatible embryonic stem cells in case of therapeutic need. This benefit can be realized only if the derivation of embryonic stem cells is successful; thus, all embryos that have undergone biopsy would have to be frozen until the results of embryonic stem-cell derivation are known. Institutional review boards would also be unlikely to approve this addition to standard IVF protocols, given the risk involved. For the procedure to be morally and politically justified, every embryo from which embryonic stem cells are derived must be given the chance to develop. How is this to be guaranteed, and who will act as the embryo recipient if, for example, 10...
embryos undergo biopsy and cell lines are derived from all of them?

All this aside, the one insurmountable problem with the approach described by Chung et al. is the unknown capacity of a single blastomere from a human embryo at the eight-cell stage to develop into a normal human. Lanza, one of the study’s authors, stated in the New York Times that viable embryos had never resulted from individual human blastomeres. This has never been tested in humans, nor will it ever be, since it would require the transfer in the uterus of a single blastomere from an eight-cell embryo to determine its developmental potential. Lanza presumably bases this assertion on the results obtained with mouse embryos, in which a blastomere from an eight-cell (as well as a four-cell)

Figure 2. Derivation of Mouse Embryonic Stem Cells from Blastocysts That Repress the Expression of Cdx2.

A recent report by Meissner and Jaenisch describes the derivation of embryonic stem cells from blastocysts that are engineered to render the blastocysts unlikely to implant into the uterus and, hence, unable to develop into a fetus. This is achieved by inserting a specific DNA cassette into a chromosome of the donor cell — that is, the cell from which the donor nucleus is derived. This DNA cassette contains a sequence that once transcribed into RNA, silences the Cdx2 gene, which is normally activated during implantation and is essential to implantation. (This RNA has a hairpin-like structure and is called “silencing” RNA.) It also contains a gene encoding green fluorescent protein. On its successful integration into a donor-cell chromosome, the Cdx2-silencing RNA is synthesized, as is the green fluorescent protein — the latter facilitates the selection of cells that have stably incorporated the DNA cassette. The donor-cell nucleus is then removed from the donor cell and injected into an enucleated ovum, which in turn develops into a blastocyst, the cells of which synthesize Cdx2-silencing RNA and green fluorescent protein. Meissner and Jaenisch showed that 40 such blastocysts failed to become implanted in pseudopregnant females — presumably owing to the repression of Cdx2 — in contrast with the successful implantation of 6 of 15 control blastocysts. Embryonic stem cells were derived from the inner cell mass of the Cdx2-repressing blastocysts and then liberated of both Cdx2-silencing RNA and green fluorescent protein through exposure to an enzyme that effectively clips the cassette from the chromosomal DNA.
embryo was unable to form a viable embryo. However, a single blastomere isolated from a rabbit or sheep embryo at the eight-cell stage is perfectly capable of developing into a normal rabbit or sheep. The same may be true for human embryos, and thus, destroying a single blastomere with the potential to develop into a human being is tantamount to destroying the entire embryo. The derivation of human embryonic stem cells from embryo biopsy will remain the moral equivalent of murder in the eyes of anyone who views any entity with the potential to develop into a human as a being with unalienable human status and rights.

Meissner and Jaenisch\(^2\) describe the derivation of mouse embryonic stem cells by the so-called altered nuclear-transfer method suggested by William Hurlbut, a member of the President’s Council on Bioethics. This method entails the creation of an embryo in which the gene essential for normal development is temporarily inactivated. Such an embryo would be deemed an entity “that lacks the attributes and capacity of a human embryo” and would be an acceptable source of embryonic stem cells, since no structure with the potential for becoming a human being would be destroyed.

Meissner and Jaenisch performed a series of elegant genetic manipulations to transiently inactivate the Cdx2 gene (essential for trophectoderm function) in the nuclear-transfer embryo by means of RNA interference (see Figure 2). They derived embryonic stem cells from these embryos and then removed the transgene producing the interfering RNA from these cells, thus reverting them to normal. There is no reason why this technique should not work in humans, so what is the problem? For the technique to be morally and politically acceptable, we must be certain that it will always produce an entity incapable of normal development, and this cannot be guaranteed for the following reasons.

First, we can only assume that Cdx2 (or any other gene that is essential for mouse development) has the same indispensable function in human development. Although likely, this assumption would have to be verified by experiments using human embryos, which would never be allowed, for ethical reasons.

Second, even assuming that we can somehow identify a gene essential for early development in humans, the method described would never allow us to be absolutely sure that each and every entity produced is incapable of normal development. Complete functional inactivation of the endogenous gene depends on the level of transcription in the embryo of the transgene encoding the interfering RNA. Since the degree of transcription of the transgene depends critically on the integration site, it would be necessary to test every single nuclear donor-cell line after nuclear transfer into the oocyte. The embryos would have to be tested for the absence of targeted RNA and for their developmental capacity. Obviously, such tests would necessitate the destruction of a certain number of nuclear-transfer embryos, some of which may have been capable of development if the expression of the transgene had not been sufficient to eliminate functional endogenous RNA.

Even if only 1 in 1000 or 1 in 1 million alternative-nuclear-transfer embryos possesses the capacity for normal development, the raison d’être of the approach collapses.

Thus, neither of the two described methods can produce human embryonic stem-cell lines that would be ideologically acceptable to the forces that assume the prerogative to decide such issues in the United States. Playing politics for the sake of science is probably necessary and sometimes noble; manipulating science for the sake of politics is usually a waste of time.
Antiretroviral Therapy in Haiti

This report presents the outcomes for the first 1004 patients with AIDS who received combination antiretroviral therapy at a clinic in Port-au-Prince, Haiti. Despite high rates of poverty, malnutrition, and tuberculosis, the outcomes were similar to those in developed countries, providing evidence in support of international efforts to make antiretroviral treatment available to people with AIDS in developing countries.

SEE P. 2325; EDITORIAL, P. 2392

Risk of Death with Conventional vs. Atypical Antipsychotic Medications

Recently, the FDA issued an advisory stating that atypical antipsychotic medications (such as olanzapine and risperidone) increase mortality among elderly patients. This study compared mortality rates among elderly patients who began using either atypical antipsychotic agents or conventional drugs (such as perphenazine and thoridazine). Conventional agents were associated with a higher rate of death. Thus, elderly patients should not be switched from atypical to conventional agents to reduce the risk of death.

SEE P. 2335; PERSPECTIVE, P. 2319

Messenger RNA for FOXP3 in the Urine of Renal-Allograft Recipients

The authors measured mRNA for the T-cell marker FOXP3, as well as for CD25, CD3e, perforin, and 18S ribosomal RNA in the urine of patients who had undergone renal transplantation, correlating results with biopsy findings and renal function. Only FOXP3 mRNA correlated inversely with serum creatinine levels in patients with acute rejection, thus providing a potentially noninvasive means of predicting outcome in acute rejection.

SEE P. 2342; EDITORIAL, P. 2394

Toxic Shock Syndrome Associated with Clostridium sordellii after Medical Abortion

The authors report four deaths due to endometritis and toxic shock syndrome associated with C. sordellii that occurred within one week after abortions that were medically induced by administration of oral mifepristone and intravaginal misoprostol. Clinical findings included tachycardia, hypotension, edema, hemocoagulation, profound leukocytosis, and absence of fever.

SEE P. 2352; PERSPECTIVE, P. 2317; CME, P. 2419

Patent Foramen Ovale in Young Adults with Unexplained Stroke

A 38-year-old man notes abrupt loss of vision in his right visual field while reading. He has no significant medical history and reports that he does not smoke or use alcohol or illicit drugs. Physical examination reveals right homonymous hemianopia but no other abnormalities. MRI reveals acute left occipital infarction and normal head and neck vessels. Transesophageal echocardiography shows a patent foramen ovale without atrial septal aneurysm. What are the implications of this finding, and what therapy should be recommended?

SEE P. 2361; CME, P. 2418

Low-Dose Aspirin for the Prevention of Atherothrombosis

This review considers the role of low-dose aspirin for the prevention of atherothrombosis, discussing the molecular mechanism of action of aspirin as well as clinical and epidemiologic studies of aspirin as an antiplatelet agent, with special emphasis on the benefits and risks in different patient populations.

SEE P. 2373; CME, P. 2417

A Hole in the Argument

An 80-year-old man presented for evaluation of shortness of breath and fatigue four weeks after repair of a hiatal hernia. He reported a mild, nonproductive cough and abdominal bloating. Before the surgery, he had been very active and had had no dyspnea.

SEE P. 2385

Public Health Principles and the HIV Epidemic

Most HIV infections are spread by persons who do not know that they are infected. This article argues that it is time to adopt the proven strategies that have contained other epidemics: widespread voluntary screening, improved notification of the partners of infected persons, and case management with close monitoring. In the United States, this approach might have the potential to prevent at least half of all cases of HIV infection each year.

SEE P. 2397
Antiretroviral Therapy in a Thousand Patients with AIDS in Haiti

Patrice Severe, M.D., Paul Leger, M.D., Macarthur Charles, M.D., Ph.D., Francine Noel, M.D., Gerry Bonhomme, M.D., Gyrlande Bois, M.D., Erik George, M.D., Stefan Kenel-Pierre, B.S., Peter F. Wright, M.D., Roy Gulick, M.D., Warren D. Johnson, Jr., M.D., Jean William Pape, M.D., and Daniel W. Fitzgerald, M.D.

ABSTRACT

BACKGROUND
The one-year survival rate of adults and children with the acquired immunodeficiency syndrome (AIDS), without antiretroviral therapy, has been about 30 percent in Haiti. Antiretroviral therapy has recently become available in Haiti and in other developing countries. Data on the efficacy of antiretroviral therapy in developing countries are limited. High rates of coinfection with tropical diseases and tuberculosis, along with malnutrition and limited laboratory monitoring of therapy, may decrease the efficacy of antiretroviral therapy in these countries.

METHODS
We studied the efficacy of antiretroviral therapy in the first 1004 consecutive patients with AIDS and without previous antiretroviral therapy who were treated beginning in March 2003 in Port-au-Prince, Haiti.

RESULTS
During a 14-month period, three-drug antiretroviral therapy was initiated in 1004 patients, including 94 children under 13 years of age. At enrollment, the median CD4 T-cell count in adults and adolescents was 131 per cubic millimeter (interquartile range, 55 to 211 per cubic millimeter); in children, a median of 13 percent of T cells were CD4-positive (interquartile range, 8 to 20 percent). According to a Kaplan–Meier survival analysis, 87 percent of adults and adolescents and 98 percent of children were alive one year after beginning treatment. In a subgroup of 100 adult and adolescent patients who were followed for 48 to 56 weeks, 76 patients had fewer than 400 copies of human immunodeficiency virus RNA per milliliter. In adults and adolescents, the median increase in the CD4 T-cell count from baseline to 12 months was 163 per cubic millimeter (interquartile range, 77 to 251 per cubic millimeter). In children, the median percentage of CD4 T cells rose from 13 percent at baseline to 26 percent (interquartile range, 22 to 36 percent) at 12 months. Treatment-limiting toxic effects occurred in 102 of the 910 adults and adolescents (11 percent) and 5 of the 94 children (5 percent).

CONCLUSIONS
This report documents the feasibility of effective antiretroviral therapy in a large number of patients in an impoverished country. Overall, the outcomes are similar to those in the United States. These results provide evidence in support of international efforts to make antiretroviral therapy available to patients with AIDS in developing countries.
ANTIRETROVIRAL THERAPY WITH THREE OR MORE MEDICATIONS IS THE INTERNATIONAL STANDARD OF CARE FOR PATIENTS WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS). In developed countries, antiretroviral therapy decreases human immunodeficiency virus (HIV) viral load, increases the CD4 T-cell count, and dramatically improves survival. However, 90 percent of the world’s 40 million people with HIV infection or AIDS live in developing countries, where high rates of coinfection with tropical diseases, tuberculosis, and malnutrition, together with limited laboratory monitoring, may decrease the efficacy of antiretroviral therapy. Since treatment has only recently become available in developing countries, data on the effects of antiretroviral therapy in these settings are limited.

We report the outcomes for the first 1000 patients with AIDS and without previous antiretroviral therapy who were treated consecutively at a clinic in Port-au-Prince, Haiti, beginning in March 2003, when international funding for antiretroviral therapy first became available. Haiti is the poorest country in the Western Hemisphere and has suffered from nearly constant political unrest for the past 20 years. AIDS was recognized in Haiti in the early 1980s. HIV infection occurs primarily through heterosexual transmission, and the prevalence is currently estimated at 3 percent in the adult population.

METHODS

Since 1983, the clinic of the Haitian Study Group for Kaposi’s Sarcoma and Opportunistic Infections (GESKIO) has provided the Port-au-Prince population, which is currently estimated at about 2 million people, with free HIV counseling, testing for HIV infection, and services for prevention of HIV infection, as well as care for patients with AIDS.

Between March 2003 and December 2004, the CD4 T-cell count was determined for all adult and adolescent patients coming to the GESKIO clinic with symptoms of HIV infection. Antiretroviral therapy, according to World Health Organization (WHO) guidelines and without regard to the perceived likelihood that the patient would adhere to the therapy, was then initiated for patients with an AIDS-defining illness or a CD4 T-cell count under 200 per cubic millimeter. The diagnosis of HIV infection in children was based on serologic testing, clinical findings, and the percentage of T cells that were CD4-positive; antiretroviral therapy was initiated in infected children according to WHO pediatric guidelines.

The full complement of personnel serving the cohort of 1004 patients described in this report consisted of five community health workers, two AIDS peer counselors, one social worker, one pharmacist, five nurses, and three physicians. The patients were routinely seen in the clinic by a physician every two weeks during the first three months of treatment and by a nurse monthly thereafter. Medications were dispensed directly to the patients on a monthly basis.

TREATMENT

First- and second-line antiretroviral-therapy regimens followed WHO guidelines, as recommended by the Haitian government. The first-line antiretroviral-therapy regimen for adults and adolescents consisted of zidovudine, lamivudine, and efavirenz. Single-drug substitutions were permitted: stavudine could be substituted for zidovudine, and nevirapine could be substituted for efavirenz. Other single-drug substitutions were permitted, according to WHO guidelines. The first-line regimen for children under 3 years of age substituted nevirapine for efavirenz.

WHO-approved generic medications constituted about 90 percent of the supply. When generic drugs were not available, brand-name medications were purchased. The cost of the three antiretroviral medications per patient per year ranged from $550 for generic medications to $750 for brand-name medications. We budgeted an additional $1,000 per patient per year to cover other costs, including personnel ($450), laboratory monitoring ($300), medications other than antiretroviral drugs ($75), data monitoring ($75), and miscellaneous other costs ($100). We estimated the overall cost per patient per year as about $1,600.

Extrapulmonary tuberculosis, but not pulmonary tuberculosis, was considered an AIDS-defining illness. HIV-infected adults and adolescents with pulmonary tuberculosis and a CD4 T-cell count of more than 200 per cubic millimeter were treated for tuberculosis, and initiation of antiretroviral therapy was deferred. In patients with tuberculosis who had a CD4 T-cell count between 50 and 200 per cubic millimeter, antiretroviral therapy was initiated after the completion of two months of tuberculosis therapy. In patients with a CD4 T-cell count of...
less than 50 cells per cubic millimeter, tuberculosis treatment and antiretroviral therapy were started simultaneously. The tuberculosis regimen consisted of two months of isoniazid, rifampin, ethambutol, and pyrazinamide daily, followed by four months of isoniazid and rifampin daily.20

Adherence to therapy was encouraged by home visits, provision of free telephone cards for patients to call clinic staff, peer counseling by people with AIDS, pill counts, and social support programs. If it was indicated, patients were referred for nutritional aid, and counseling was offered to pregnant women, parents of HIV-infected children, and victims of domestic violence. Directly observed antiretroviral therapy, which has been very effective in rural Haiti,21 was not feasible for our urban patients, who have limited social networks and frequently change their addresses.

CLINICAL MEASUREMENTS
Body weight was measured at every visit. The z score for weight for children was reported as the number of standard deviations above or below the median weight for age. Laboratory monitoring included the baseline CD4 T-cell count by flow cytometry (Becton Dickinson) and measurement of hemoglobin. The CD4 T-cell count was determined every six months. Follow-up hemoglobin measurements, liver-function tests, and serum chemical analyses were performed if clinically indicated. The level of HIV RNA in plasma at 12 months was determined in a subgroup of all available adult and adolescent patients who had been followed up for 48 to 56 weeks in December 2004. The Amplicor HIV-1 Monitor PCR Test (Roche), with a lower limit of detection of 400 copies of HIV RNA per milliliter, was used.

STATISTICAL ANALYSIS
The institutional review boards at GHESKIO and at Weill Medical College of Cornell University approved this study. We collected data from an electronic medical record and from the charts of patients with AIDS in whom three-drug antiretroviral therapy had been initiated between March 1, 2003, and April 30, 2004. Follow-up data collected through December 31, 2004, were included. The data were analyzed by an intention-to-treat approach with the use of SAS software. Proportions were compared by the chi-square test with Yates’ correction or, for expected cell values of less than five, by Fisher’s exact test. Means and medians were compared by Student’s t-test and the Wilcoxon rank-sum test, respectively. Kaplan–Meier survival analyses were used to estimate the time from the initiation of antiretroviral therapy to death and the time from initiation to the first treatment-limiting toxic drug effect. For patients who did not reach the end point, the data were censored at the date of the last visit. The log-rank test was used to compare survival times between strata. The Cox proportional-hazards model was used for multivariate analysis. Variables associated with mortality in previous publications or in our clinical experience were included in the initial model. Variables were removed from the model by a backward selection procedure if the value of alpha was greater than 0.05. Confounders causing a 10 percent change in another predictor were left in the model.

RESULTS

ENROLLMENT
Between March 1, 2003, and April 30, 2004, GHESKIO provided HIV counseling, testing, and primary care to 23,394 patients, of whom 3978 (17 percent) were HIV-seropositive. Of these HIV-infected patients, 1004 (25 percent) who had not previously received treatment met the criteria for antiretroviral therapy, and therapy was initiated in these patients; 2778 (70 percent) had early-stage HIV disease and did not require antiretroviral therapy; 57 (1 percent) met the criteria for antiretroviral therapy but were lost to follow-up before therapy could be initiated; 129 (3 percent) had previously received antiretroviral therapy; and 10 (<1 percent) died after they were tested for HIV and before antiretroviral therapy could be initiated (Fig. 1). The mean enrollment rate was 80 new patients per month (range, 32 to 141). Enrollment continued after April 2004, and approximately 2500 patients are currently receiving antiretroviral therapy at GHESKIO. The baseline characteristics of the first 1004 patients and their initial antiretroviral-therapy regimens are provided in Table 1.

DISPOSITION OF PATIENTS AT THE TIME OF DATA ANALYSIS
At the time of data analysis, 800 of the 1004 patients (80 percent) were still being followed up, 75 (7 percent) had been lost to follow-up, and 129 (13 percent) had died. There was no difference in baseline characteristics (including age, sex, CD4 T-cell count, body weight, and stage of HIV infection) be-
between patients who were lost to follow-up and those who were not. The most common reason for patients’ becoming lost to follow-up was their leaving Port-au-Prince to return to their rural villages. The median follow-up time for the 1004 patients was 13 months. The cohort profile is shown in Figure 1.

**Survival**

Of the 910 adult and adolescent patients, 127 (14 percent) died. Of the 127 deaths, 55 (43 percent) were due to persistent wasting syndrome, 20 (16 percent) to tuberculosis, 6 (5 percent) to bacterial pneumonia, 5 (4 percent) to toxoplasmosis, 4 (3 percent) to cancer, 4 (3 percent) to cryptosporidiosis, 4 (3 percent) to sepsis syndrome, 3 (2 percent) to congestive heart failure, 3 (2 percent) to trauma, and 23 (18 percent) to unknown causes. One hundred of the 127 deaths (79 percent) occurred within six months after the initiation of antiretroviral therapy. According to survival analysis, 90 percent of the patients were alive at 6 months and 87 percent at 12 months (Fig. 2). The factors present at the initiation of antiretroviral therapy that were predictors of death were the presence of an AIDS-defining ill-
**Table 1.** Baseline Characteristics of Patients in Haiti Receiving Antiretroviral Therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults and adolescents (N=910)</strong></td>
<td></td>
<td><strong>Children (N=94)</strong></td>
<td></td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>504 (55)</td>
<td>Female sex — no. (%)</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Age — no. (%)</td>
<td></td>
<td>Age — no. (%)</td>
<td></td>
</tr>
<tr>
<td>13–19 yr</td>
<td>30 (3)</td>
<td>&lt;1 yr</td>
<td>4 (4)</td>
</tr>
<tr>
<td>20–29 yr</td>
<td>120 (13)</td>
<td>1–4 yr</td>
<td>34 (36)</td>
</tr>
<tr>
<td>30–39 yr</td>
<td>352 (39)</td>
<td>5–12 yr</td>
<td>56 (60)</td>
</tr>
<tr>
<td>40–49 yr</td>
<td>290 (32)</td>
<td>Status of parents†</td>
<td></td>
</tr>
<tr>
<td>&gt;49 yr</td>
<td>118 (13)</td>
<td>Both dead</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Resident of Port-au-Prince — no. (%)</td>
<td>816 (90)</td>
<td>1 Dead</td>
<td>41 (44)</td>
</tr>
<tr>
<td>Self-referred — no. (%)</td>
<td>419 (46)</td>
<td>Both alive</td>
<td>39 (41)</td>
</tr>
<tr>
<td>Income &lt; $1/day — no. (%)</td>
<td>513 (56)</td>
<td>AIDS-defining illness — no. (%)</td>
<td>44 (47)</td>
</tr>
<tr>
<td>Education — no. (%)</td>
<td></td>
<td>Tuberculosis — no. (%)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>None</td>
<td>157 (17)</td>
<td>z Score for weight</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>281 (31)</td>
<td>Median</td>
<td>–1.8</td>
</tr>
<tr>
<td>Secondary school</td>
<td>404 (44)</td>
<td>Interquartile range</td>
<td>–2.6 to –1.1</td>
</tr>
<tr>
<td>College</td>
<td>68 (7)</td>
<td>CD4 T cells — %</td>
<td></td>
</tr>
<tr>
<td>Marital status — no. (%)</td>
<td></td>
<td>Median</td>
<td>13</td>
</tr>
<tr>
<td>Common-law marriage</td>
<td>285 (31)</td>
<td>Interquartile range</td>
<td>8 to 20</td>
</tr>
<tr>
<td>Married</td>
<td>162 (18)</td>
<td>Hemoglobin — g/dl</td>
<td></td>
</tr>
<tr>
<td>Separated</td>
<td>159 (17)</td>
<td>Median</td>
<td>9.5</td>
</tr>
<tr>
<td>Single</td>
<td>209 (23)</td>
<td>Interquartile range</td>
<td>8.8 to 10.2</td>
</tr>
<tr>
<td>Widowed</td>
<td>95 (10)</td>
<td>Initial antiretroviral-therapy regimen — no. (%)</td>
<td></td>
</tr>
<tr>
<td>AIDS-defining illness — no. (%)</td>
<td>472 (52)</td>
<td>Zidovudine, lamivudine, efavirenz</td>
<td>58 (62)</td>
</tr>
<tr>
<td>Tuberculosis — no. (%)</td>
<td>72 (8)</td>
<td>Zidovudine, lamivudine, nevirapine</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Pregnant — no. (%)</td>
<td>22 (2)</td>
<td>Didanosine, lamivudine, efavirenz</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Body weight — kg</td>
<td></td>
<td>Other</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Men</td>
<td>55.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>48.9 to 62.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>48.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>43.0 to 55.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 T-cell count — per mm$^3$</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>55 to 211</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin — g/dl</td>
<td>10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>9.2 to 11.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial antiretroviral-therapy regimen — no. (%)</td>
<td></td>
<td>Zidovudine, lamivudine, efavirenz</td>
<td>58 (62)</td>
</tr>
<tr>
<td>Zidovudine, lamivudine, efavirenz</td>
<td>428 (47)</td>
<td>Zidovudine, lamivudine, nevirapine</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Zidovudine, lamivudine, abacavir</td>
<td>381 (42)</td>
<td>Didanosine, lamivudine, efavirenz</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>48 (5)</td>
<td>Other</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

* AIDS-defining illnesses are those listed by the World Health Organization.†

† One third of surviving HIV-infected parents were also receiving antiretroviral therapy.
ness, a CD4 T-cell count under 50 per cubic millimeter, and a body weight in the lowest quartile for sex (Table 2).

Two of the 94 children died within one month after enrollment, one from a sepsis-like syndrome and the other from a respiratory tract infection of unknown cause. According to survival analysis, 98 percent of the cohort was alive at one year.

**OTHER MEASURES OF TREATMENT RESPONSE**

**Virologic Response**

Plasma HIV RNA was measured in adult and adolescent patients who had a 1-year follow-up visit (at 48 to 56 weeks) in December 2004. Plasma was available from 100 of the 117 adult and adolescent patients who had been followed for one year (85 percent). Viral load was less than 400 copies of HIV RNA per milliliter in 76 of the 100 patients tested. There were no significant differences in baseline characteristics between the 76 patients with fewer than 400 copies of HIV RNA per milliliter and the 24 patients with 400 or more copies per milliliter.

**CD4 T-Cell Response**

In adults and adolescents, the median increase in the CD4 T-cell count at six months was 128 per cubic millimeter (interquartile range, 62 to 197 per cubic millimeter). The CD4 T-cell count at six months was greater than the baseline value in 459 of 504 patients (91 percent) and remained the same or decreased from baseline in 45 (9 percent). The median increase in the CD4 T-cell count at 12 months was 163 per cubic millimeter (interquartile range, 77 to 251 per cubic millimeter). The CD4 T-cell count at 12 months was greater than the baseline value in 360 of 397 patients (91 percent) and remained the same or decreased from baseline in 37 (9 percent). In children, the median CD4 T-cell percentage rose from a baseline value of 13 percent (interquartile range, 8 to 20 percent) to 21 percent (interquartile range, 16 to 29 percent) at 6 months and to 26 percent (interquartile range, 22 to 36 percent) at 12 months.

**Weight Gain**

At six months, adult and adolescent patients had gained a median of 4.0 kg (interquartile range, 0.9 to 7.7). At six months, 639 of 759 patients (84 percent) had gained weight, and 120 patients (16 percent) remained at the same weight or had lost weight. At 12 months, adult and adolescent patients had gained a median of 5.5 kg (interquartile range, 1.4 to 10.5). At 12 months, 396 of 466 patients (85 percent) had gained weight, and 70 (15 percent) remained at the same weight or had lost weight. In children, the z score for weight increased from a median value of −1.8 (interquartile range, −2.6 to −1.1) at enrollment, to −1.3 at 6 months (interquartile range, −1.9 to −0.6) and to −1.2 at 12 months (interquartile range, −1.6 to −0.4).

**Tuberculosis**

Of the 910 adult and adolescent patients, 113 (12 percent) received concurrent treatment for tuberculosis while receiving antiretroviral therapy, 72 (8 percent) began treatment for tuberculosis before beginning antiretroviral therapy, and 41 (5 percent) began treatment for tuberculosis after beginning antiretroviral therapy. Two patients with CD4 T-cell counts of 50 to 200 per cubic millimeter started tuberculosis treatment but died in the two-month period before they would have begun antiretroviral therapy (Fig. 1). Of the 113 patients who received concurrent treatment for tuberculosis while receiving antiretroviral therapy, 89 (79 percent) were cured of tuberculosis, 20 (18 percent) died, 1 (1 percent) did not respond to tuberculosis therapy, and 3 (3 percent) were lost to follow-up. There was no significant difference in survival between patients with and patients without tuberculosis.

Of the 72 patients who started tuberculosis treatment before antiretroviral therapy, 11 (15 percent) had a suspected immune reconstitution syn-
drome with temporary worsening of tuberculosis symptoms after beginning antiretroviral therapy, including recurrent fevers, increasing cough, and a draining lymph-node fistula; 4 were treated with corticosteroids. No patient stopped antiretroviral therapy because of the immune reconstitution syndrome.

Forty-one patients were found to have tuberculosis after beginning antiretroviral therapy; symptoms of tuberculosis commenced within three months after the initiation of antiretroviral therapy in 26 (63 percent). A weight loss of more than 5 percent at month 3 was associated with the diagnosis of tuberculosis after the initiation of antiretroviral therapy (odds ratio, 2.62; 95 percent confidence interval, 1.17 to 5.86; P=0.04).

Among the 94 children, 13 (14 percent) received antiretroviral therapy with concurrent treatment for tuberculosis. Eleven of these 13 children (85 percent) appeared to have been cured of tuberculosis, and 2 (15 percent) were lost to follow-up; none of them died. There was no significant difference in survival between children with and without tuberculosis.

**FIRST-LINE MEDICATION CHANGES AND TOXIC EFFECTS**

Of the 910 adult and adolescent patients, 229 (25 percent) required a change in a first-line medication. The reasons for the change were toxic effects in 102 patients (11 percent), disruption in the medication supply in 66 patients (7 percent), sexual activity by women of reproductive age in 29 patients (3 percent), suspected treatment failure in 11 patients (1 percent), and tuberculosis in 21 patients (2 percent). The disruptions in medication supply occurred when international suppliers were months late in delivering medications.

Table 3 shows the treatment-limiting toxic effects of first-line medications. Anemia and central nervous system symptoms were the most common. Two patients had the Stevens–Johnson syndrome, one of whom died; nevirapine was the suspected cause in both cases. Gynecomastia, in several cases accompanied by lactorrhea, occurred in 15 men receiving efavirenz. According to Kaplan–Meier survival analysis, 14 percent of the adult and adolescent patients required a change in first-line medication because of a toxic effect during the first 12 months of antiretroviral therapy.

Of the 94 children, 9 (10 percent) required a medication change: 5 because of toxic effects, 1 because of a disruption in medication supply, and 3 because of tuberculosis treatment. Of the five children whose medication was changed because of a toxic effect, two receiving zidovudine had anemia, one receiving nevirapine had a rash, one receiving efavirenz had hepatitis, and one receiving efavirenz had gynecomastia.

**DISCUSSION**

Antiretroviral therapy was initiated in 1004 patients with AIDS within 14 months after international funds for therapy became available in Haiti. This large cohort was consecutively enrolled, had high rates of poverty, malnutrition, and tuberculosis, and was similar to clinic populations that would be found in other urban areas severely affected by HIV disease in the Caribbean or sub-Saharan Africa. The one-year survival was 87 percent for adults and adolescents and 98 percent for children. In comparison, the one-year survival without antiretroviral therapy for adults and children with AIDS in Haiti and other developing countries is about 30 percent.22-24 This rapid and effective large-scale introduction of antiretroviral therapy in the poorest country in the Western Hemisphere, even during times of political unrest, provides evidence in support of international efforts to make antiretroviral therapy available to patients with AIDS worldwide.

The virologic response rate of 76 percent (with a response defined as <400 copies of HIV RNA per milliliter) and the median increase in the CD4 T-cell count of 163 per cubic millimeter at one year in adults and adolescents are similar to results from the United States. In a meta-analysis of clinical trials involving adults not previously treated with antiretroviral therapy who received a three-drug antiretroviral-therapy regimen that included a nonnucleoside reverse-transcriptase inhibitor,
The virologic response rate (<400 copies of HIV RNA per milliliter) at 48 weeks was 72 percent and the mean increase in the CD4 T-cell count was 174 per cubic millimeter.25,26 An analysis of the 12-month outcomes of patients beginning antiretroviral therapy in 2001 and 2002 in a Baltimore clinic found a virologic response rate (<400 copies of HIV RNA per milliliter) of 68 percent and a mean increase in the CD4 T-cell count of 139 per cubic millimeter.27,28 

The rates of treatment-limiting toxic effects in our patients were similar to those reported for patients from developed countries who were treated with similar regimens.29,30 Despite recent concern about nevirapine toxicity,31 less than 1 percent of the patients in our cohort who were treated with nevirapine had hepatitis. Nevirapine-induced hepatitis has been associated with a CD4 T-cell count of more than 250 per cubic millimeter, but the count in most of our patients was less than 200 per cubic millimeter. Among the patients who began therapy with efavirenz, treatment-limiting toxic effects occurred in 10 percent, a rate higher than that reported from the United States. Most Haitians are of African descent, and a recent study demonstrated that people of African descent are at greater risk than others for central nervous system side effects from efavirenz.32 An additional 6 percent of patients who began therapy with efavirenz stopped because of the risk of teratogenicity in sexually active women. Alternatives to first-line regimens containing efavirenz may be especially important for populations of African origin with large numbers of sexually active women.

The challenges involved in providing antiretroviral therapy in developing countries include high rates of poverty, malnutrition, and tuberculosis. The majority of our patients earned less than $1 a day, the World Bank’s international poverty line.33 Poverty affects all aspects of care, including patients’ ability to buy food, obtain access to clean water and housing, and pay for transportation to the clinic. We have therefore striven to integrate our antiretroviral-therapy program with existing social programs. There is a growing body of evidence that malnutrition is a critical cofactor in AIDS progression in resource-poor countries.34,35 In our cohort, low baseline body weight was an independent predictor of death. We therefore provided a daily multivitamin supplement to all of our patients who were receiving antiretroviral therapy and a monthly stock of rice, beans, and vegetable oil to the most undernourished patients. Twelve percent of our patients who were receiving antiretroviral therapy received concurrent treatment for tuberculosis. Data from this study suggest that a failure to gain weight after three months of antiretroviral therapy should prompt an evaluation for tuberculosis. Patients with tuberculosis had a survival rate similar to that of patients without tuberculosis.

The single greatest logistic challenge was maintaining the supply of antiretroviral drugs. Delays in delivery resulted in a change in the antiretroviral-therapy regimen for 7 percent of our patients. Developing reliable manufacturing and distribution systems for antiretroviral drugs is an urgent international priority. Other logistic challenges may arise in different developing countries.

We estimated the overall cost of treating a patient with antiretroviral therapy to be about $1,600 per year, with antiretroviral medications accounting for 35 to 45 percent of the total. The care of the 1004 patients receiving antiretroviral therapy was supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria and the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). However, there are a number of other, intangible factors that significantly contributed to the successful implementation of this program, including continuity of

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients Initiating Treatment</th>
<th>Toxic Effect</th>
<th>Patients Stopping Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>866</td>
<td>Anemia</td>
<td>41 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis*</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>401</td>
<td>Rash†</td>
<td>11 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis*</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>55</td>
<td>Rash</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* Both cases of hepatitis occurred in patients who were receiving concurrent treatment for tuberculosis.
† Two patients with the Stevens–Johnson syndrome are included.
leadership, international collaboration, and dedication of GHESKIO personnel who provided care to poor patients with AIDS in an urban slum, even during times of violent political unrest. These factors are the product of infrastructure development, personnel training, and mentorship, which are critical for scaling up antiretroviral therapy. The treatment outcomes achieved in Haiti were similar to those achieved in U.S. clinics, providing evidence in support of international efforts to make antiretroviral therapy available in developing countries. Finally, the sustainability of programs in Haiti and in other impoverished countries is absolutely dependent on continued international support.

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REFERENCES

Boehringer Ingelheim, February 2004 (letter to health care professionals).


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Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

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BACKGROUND
Recently, the Food and Drug Administration (FDA) issued an advisory stating that atypical antipsychotic medications increase mortality among elderly patients. However, the advisory did not apply to conventional antipsychotic medications; the risk of death with these older agents is not known.

METHODS
We conducted a retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in Pennsylvania and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2003. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication. We controlled for potential confounding variables with the use of traditional multivariate Cox models, propensity-score adjustments, and an instrumental-variable analysis.

RESULTS
Conventional antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications at all intervals studied (≤180 days: relative risk, 1.37; 95 percent confidence interval, 1.27 to 1.49; <40 days: relative risk, 1.56; 95 percent confidence interval, 1.37 to 1.78; 40 to 79 days: relative risk, 1.37; 95 percent confidence interval, 1.19 to 1.59; and 80 to 180 days: relative risk, 1.27; 95 percent confidence interval, 1.14 to 1.41) and in all subgroups defined according to the presence or absence of dementia or nursing home residency. The greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotic medications. Increased risks associated with conventional as compared with atypical antipsychotic medications persisted in confirmatory analyses performed with the use of propensity-score adjustment and instrumental-variable estimation.

CONCLUSIONS
If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning.
Antipsychotic medications are disproportionately used among elderly persons and are prescribed for more than a quarter of Medicare beneficiaries in nursing homes. The conditions for which these agents are prescribed include dementia, delirium, psychosis, agitation, and affective disorders, with many of the prescriptions being written for indications that have not been approved by the Food and Drug Administration (FDA). In addition to increasing use, there have been rapid shifts from first-generation conventional agents (e.g., phenothiazines and butyrophenones) to heavily marketed second-generation atypical agents (e.g., aripiprazole [Abilify], clozapine [Clozaril], olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal], and ziprasidone [Geodon]).

In a Public Health Advisory issued in April 2005, the FDA warned that the use of atypical antipsychotic medications nearly doubled the risk of death, as compared with the risk with placebo, in 17 short-term, randomized, controlled trials involving elderly persons with dementia. “Black box” warnings describing this risk and advising that the atypical antipsychotic medications were not approved for use in elderly patients with dementia were added to the labels of all such agents. The advisory did not extend to conventional antipsychotic medications, although the FDA noted that the risk associated with these agents is an important issue for future study.

In the absence of data regarding the risk of death posed by conventional antipsychotic medications, there is mounting concern that clinicians may simply switch elderly patients to these older agents, particularly since their replacement by the newer drugs occurred so rapidly and recently. Mainly on the basis of extrapolations from studies involving younger populations, some investigators have suggested that conventional antipsychotic medications could, in theory, pose risks equal to or greater than those associated with the newer drugs in older populations.

We sought to define the risk of death in the short term among elderly patients who were beginning therapy with conventional antipsychotic medications, as compared with the risk among those beginning treatment with atypical antipsychotic agents. We also examined whether the risk of death differed according to the dosage of conventional antipsychotic medications, the presence or absence of dementia, and whether or not the patient resided in a nursing home. The underlying reasons for using both types of drugs (e.g., to treat dementia or delirium) may themselves be risk factors for death. Therefore, we restricted our analysis to patients who were given an antipsychotic medication. In addition, we restricted the analysis to new users in order to guard against selection bias among those already using antipsychotic medications from early emergence of symptoms, drug intolerance, or treatment failure. To control for potential differences in the characteristics of patients who were prescribed different antipsychotic medications, we used traditional multivariate and propensity-score–adjusted Cox proportional-hazards models as well as instrumental-variable estimation. In sensitivity analyses, we examined the degree to which a hypothetical confounder would have to be related to the use of a conventional antipsychotic medication and to mortality to cause a spurious increase in the apparent risk associated with conventional agents if none truly existed.

Methods

Sources of Data
The Pharmaceutical Assistance Contract for the Elderly Information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE), a large state prescription-benefits program for the elderly in the United States, was available from January 1, 1994, through December 31, 2003. PACE has no deductibles or maximum annual benefit and charges a modest copayment of $6 for each prescription. The income ceiling for eligibility is $14,000 per year for single persons and $17,200 per year for couples, resulting in a recipient population of both indigent and near-poor elderly persons. These generous benefits and requirements for financial need result in essentially no out-of-pocket (i.e., out-of-system) medication use.

Pennsylvania Medicare
Medicare data included both Part A (covering hospitalizations and nursing home stays) and Part B (covering outpatient services and procedures) for all PACE enrollees from January 1, 1994, through December 31, 2003. Medicare data on mortality were drawn from the Death Master File, which undergoes extensive verification and weekly updates by the Social Security Administration.
We assembled data for all filled prescriptions, procedures, physician encounters, hospitalizations, and long-term care into a relational database. All traceable, person-specific identifying factors were transformed into anonymous, coded study numbers to protect subjects’ privacy. The study was approved by the institutional review board of Brigham and Women’s Hospital.

**STUDY POPULATION**

All subjects were 65 years of age or older and filled a first recorded (index) prescription for an oral antipsychotic medication between January 1, 1994, and December 31, 2003. To ensure a uniform six-month eligibility period before the index prescription for antipsychotic medication was filled, all study subjects were required to have used at least one medical service (e.g., a physician visit, procedure, or hospitalization) and filled at least one prescription, both within the six months before the index date and in the time period preceding the six months before the index date.

**ANTIPSYCHOTIC MEDICATIONS**

Atypical antipsychotic agents included aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon). Other antipsychotic medications were considered to be conventional agents, including acetophenazine (Tindal), chlorpromazine (Thorazine), fluphenazine (Prolixin, Permitil), mesoridazine (Sertil), perphenazine (Trilafon), thioridazine (Mellaril), trifluoperazine (Stelazine), triflupromazine (Vesprin), chlorprothixene (Taractan), haloperidol (Haldol), loxapine (Loxitane), molindone (Moban), pimozide (Orap), and thiothixene (Navane). We also investigated whether a dose–response relationship existed in adjusted models by separating antipsychotic medications within these intervals. Adjusted models were analyzed separately in subgroups defined according to the presence or absence of dementia and nursing home residency. Other conditions included cerebrovascular disease (e.g., both cerebral hemorrhagic and ischemic events), congestive heart failure, myocardial infarction, other evidence of ischemic heart disease (e.g., angina, percutaneous transluminal coronary angioplasty, coronary-artery bypass grafting, or use of nitroglycerin), other cardiovascular conditions (e.g., valvular disease, aneurysms, or peripheral vascular disease), cancer, human immunodeficiency virus (HIV) infection, dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders. The use of health care services that were potentially predictive of a higher or lower risk of death in the short term were also assessed; these included hospitalizations, nursing home stays, the use of other psychiatric medications, and the total number of medications used (excluding antipsychotic agents and drugs used to define covariates).26

**OTHER VARIABLES**

We defined the characteristics of the patients during the six months before each subject’s index date according to demographic data (age, sex, and race), coexisting illnesses, and use of health care. To define clinical conditions that may have been associated with a higher or lower risk of death in the short term, we used the diagnostic codes of the International Classification of Diseases, 9th Revision, Clinical Modification,23 the procedure codes of Physicians’ Current Procedural Terminology,24 and diagnosis-related group hospital-discharge codes,25 and we assessed medication use. For example, arrhythmias were defined according to the presence of ventricular arrhythmias and diagnoses of other cardiac arrhythmias and the use of an antiarrhythmia medication. Similarly, diabetes was defined according to previous diagnoses plus the use of medications for the treatment of diabetes. Other conditions included cerebrovascular disease (e.g., both cerebral hemorrhagic and ischemic events), congestive heart failure, myocardial infarction, other evidence of ischemic heart disease (e.g., angina, percutaneous transluminal coronary angioplasty, coronary-artery bypass grafting, or use of nitroglycerin), other cardiovascular conditions (e.g., valvular disease, aneurysms, or peripheral vascular disease), cancer, human immunodeficiency virus (HIV) infection, dementia, delirium, mood disorders, psychotic disorders, and other psychiatric disorders. The use of health care services that were potentially predictive of a higher or lower risk of death in the short term were also assessed; these included hospitalizations, nursing home stays, the use of other psychiatric medications, and the total number of medications used (excluding antipsychotic agents and drugs used to define covariates).26

**Statistical Analysis**

We calculated distributions of demographic and clinical characteristics and use of medications among subjects receiving conventional and atypical antipsychotic agents and then plotted mortality rates during the first 180 days after the initiation of therapy with a drug from either class. A 180-day follow-up period was chosen on the basis of the duration of trials in the FDA’s reanalysis (which ranged from 4 to 26 weeks, with a modal duration of 10 weeks).6 Unadjusted and multivariate Cox proportional-hazards models (controlled for calendar year and all variables listed above) were constructed for deaths occurring within 180 days after the initiation of therapy. Models of death within less than 40 days, 40 to 79 days, and 80 to 180 days were also constructed after a visual inspection of plots of death rates revealed roughly proportional hazards among users of conventional and atypical antipsychotic medications within these intervals. Adjusted models were analyzed separately in subgroups defined according to the presence or absence of dementia and nursing home residency. We also investigated whether a dose–response relationship existed in adjusted models by separating users of conventional antipsychotic medications into subgroups made up of those taking the median daily dose or less and those taking more than the median daily dose.
In confirmatory analyses, we used the Cox models again with propensity-score adjustments to balance independent risk factors for death between the groups of drug users. Propensity scores were derived from predicted probabilities in logistic-regression models of the use of conventional as compared with atypical antipsychotic medications. The final nonparsimonious model contained all variables shown in Table 1 and strongly predicted the type of antipsychotic medication used (C statistic = 0.845). We then stratified Cox models of mortality across deciles of the propensity score.

We also used instrumental-variable analysis to provide estimates that would remain unbiased even if important confounding variables were not measured. An instrumental variable is an observable factor related to treatment choice but unrelated to characteristics of patients or to outcomes. As in other recent work, we used the prescribing physician’s preference for conventional or atypical antipsychotic medications (as indicated by his or her most recent new prescription for an antipsychotic agent) as the instrument. We operationalized the instrumental variable as the choice of medication made by each prescribing physician for his or her most recent patient newly started on an antipsychotic medication before the index prescription was written. Using two-stage linear regression for the estimation of instrumental variables and additional adjustment for measured characteristics of the patients, we calculated the difference in the risk of death within 180 days between subjects receiving conventional antipsychotic medications and those receiving atypical agents. Finally, we performed a sensitivity analysis to determine the degree to which a hypothetical confounder would have to be related to the use of a conventional antipsychotic medication as well as to mortality to cause a spurious increase in the apparent risk associated with the use of conventional antipsychotic agents if none truly existed.

**RESULTS**

Table 1 shows the characteristics of the 22,890 new users of conventional or atypical antipsychotic agents. The 9142 patients who began using conventional antipsychotic agents were slightly younger and more likely to be male and nonwhite than were the 13,748 who began using atypical antipsychotic drugs. New users of the conventional agents were less likely than new users of the atypical agents to have cerebrovascular disease, dementia, delirium, psychoses, or other psychiatric disorders but more likely to have congestive heart failure, ischemic heart disease other than myocardial infarction, or cancer. Users of conventional agents had lower rates of use of antidepressant agents and other psychotropic medications, a lower total number of drugs used, and lower rates of hospitalization and nursing home stays within the previous 180 days. In the first 180 days of use, 17.9 percent of patients who began using conventional antipsychotic medications died, as compared with 14.6 percent of those who began using atypical agents.

The relative risk of death among new users of conventional drugs, as compared with new users of atypical drugs, is shown in Table 2. The risk of death was significantly higher for conventional agents than for atypical agents in both unadjusted analyses of death within 180 days and in adjusted analyses in which we controlled for a large number of potential confounders. The greatest increase in the adjusted risk of death for conventional as compared with atypical antipsychotic medications occurred with higher doses (i.e., greater than the median) of conventional agents and during the first 40 days after the initiation of therapy. In analyses among subgroups defined by the presence or absence of dementia or residency in a nursing home, patients who began using conventional antipsychotic agents had a significantly higher risk of death within 180 days, in all subgroups studied, than did those who began using atypical agents (Table 2). Figure 1 shows mortality rates (in deaths per person-year) over the first 180 days after the beginning of therapy with antipsychotic medications. Consistent with our adjusted models of mortality during specific periods, we observed that the increased rates of death associated with conventional as compared with atypical antipsychotic agents were greatest soon after therapy was initiated; the rates of death then began converging in subsequent periods.

Confirmatory analyses with the use of propensity-score adjustments yielded no substantive differences relative to traditional multivariate Cox analyses. For example, the hazard ratio for death within 180 days for conventional as compared with atypical antipsychotic medications in a Cox model with the use of deciles of propensity scores to balance covariables was 1.37 (95 percent confidence interval, 1.27 to 1.49). The hazard ratio remained stable and without trend (ranging between 1.17 and 1.58) across separate Cox analyses.
performed within each decile of the propensity score.

In instrumental-variable analyses, conventional agents continued to be associated with a higher risk of death within 180 days than did atypical agents. The difference in risk of 0.073 (95 percent confidence interval, 0.020 to 0.126) meant that on average, for every 100 patients treated with a conventional antipsychotic drug instead of an atypical agent, there would be 7 additional deaths. Sensitivity analyses revealed that very large relative risks — of 7 or more — would be needed, linking a hypothetical confounder to both the use of conventional agents and mortality, to explain fully the increased observed risk of death associated with the use of conventional agents, if no risk truly existed.

In this study of 22,890 elderly persons beginning therapy with antipsychotic medications, patients for whom conventional agents were prescribed had a 37 percent higher, dose-dependent risk of death in the short term than those for whom atypical agents were prescribed. To place this magnitude of risk in perspective, only cancer, congestive heart failure, and HIV infection conferred greater adjusted risks in our analyses. Unfortunately, there are few studies of death associated with drugs in the elderly with which to compare our results; one observational study found higher rates of death among those given a conventional drug (haloperidol) than among those given one of two atypical drugs (risperidone or olanzapine).

If confirmed, our results suggest that conventional antipsychotic medications may not be safer than atypical agents and should not simply replace atypical drugs that are stopped in response to recent FDA warnings, as may be happening. It is important to assess whether methodologic limitations, rather than true biologic relationships, might explain these findings. Confounding would occur if conventional drugs were more likely than atypical agents to be given to patients who were more frail or at greater risk of dying than others. Therefore, using traditional multivariate, propensity-score, and instrumental-variable techniques, we controlled for the demographic and clinical factors and use of health care services that were likely to be independent predictors of death. We also restricted our analyses to only those patients who had used antipsychotic agents as well as to those who were new users, to control for the underlying reasons that patients use antipsychotic medications and for any selection bias from early emergence of symptoms, drug intolerance, or treatment failure among those already using antipsychotic medications.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Users of Conventional Antipsychotic Medications (N=9142)</th>
<th>Users of Atypical Antipsychotic Medications (N=13,748)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>83.2</td>
<td>83.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77.6</td>
<td>83.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>22.4</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92.8</td>
<td>94.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>7.2</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1.4</td>
<td>1.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>29.1</td>
<td>30.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>32.6</td>
<td>31.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.8</td>
<td>26.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.5</td>
<td>3.5</td>
<td>0.85</td>
</tr>
<tr>
<td>Other ischemic heart disease</td>
<td>29.3</td>
<td>24.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other cardiovascular disorders</td>
<td>12.7</td>
<td>12.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Cancer</td>
<td>15.6</td>
<td>14.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV infection</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Dementia</td>
<td>40.8</td>
<td>52.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delirium</td>
<td>12.2</td>
<td>16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>22.2</td>
<td>36.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>21.3</td>
<td>24.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other psychiatric disorders</td>
<td>5.9</td>
<td>8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of other drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>28.0</td>
<td>43.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other psychotropic medications</td>
<td>11.5</td>
<td>13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total no. of drugs used (mean)</td>
<td>6.8</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization in previous 180 days</td>
<td>51.2</td>
<td>53.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nursing home residence in previous 180 days</td>
<td>15.9</td>
<td>21.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death within 180 days of index prescription for antipsychotic medication</td>
<td>17.9</td>
<td>14.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Race was self-reported.
indications for frail elderly persons, any residual confounding may have led to an underestimation of mortality resulting from the use of conventional agents. Any misclassification of exposure status that occurred nondifferentially with respect to the class of antipsychotic agent (e.g., a lack of consumption of filled prescriptions or a switch from a conventional to an atypical antipsychotic agent, or vice versa) would bias results toward the null; differential misclassification (e.g., decreased adherence among patients taking conventional agents, as has been found\textsuperscript{29}) may have led to an underestimation of the rates of death associated with conventional agents. Misclassification of information from Medicare with regard to mortality is less likely, given the Social Security Administration’s extensive verification process for data from the Death Master File,\textsuperscript{21} and such misclassification would presumably bias our findings toward the null.

Finally, we controlled for calendar time, to adjust for any improvements in health care over the study period that could lead to improved survival in later years, when the use of atypical drugs would be more common. However, in spite of these safeguards and the convergence of results from confirmatory and sensitivity analyses, it is important to keep in mind that our study is based on nonexperimental data. There may be other factors with regard to patients who were newly prescribed conventional antipsychotic medications that we were unable to control for, requiring a circumspect interpretation of these findings.

Potential mechanisms through which conventional antipsychotic medications might increase the risk of death in the short term are unclear, and the causes of death were unavailable. In the FDA analysis on which the April 2005 advisory was based, heart-related events (e.g., heart failure and sudden death) and infections (mostly pneumonia) accounted for most deaths.\textsuperscript{6} Anticholinergic properties (affecting blood pressure and heart rate), prolongation of the QT interval (causing conduction delays), and extrapyramidal symptoms (causing swallowing problems) are at least as common with conventional drugs as with atypical agents, and probably more so, and should be investigated as potential underlying causes of death.\textsuperscript{4,9–12} Whatever the underlying cause or causes are, they most markedly elevate the risk of death with the use of conventional as compared with atypical antipsychotic medications immediately after the initiation of therapy, after which their influence subsides somewhat. The hazard ratios associated with conventional as compared with atypical agents were not confined to high-risk elderly persons with dementia or those residing in nursing homes. However, because the clinical trials that the FDA initially reviewed exclu-

### Table 2. Relative Risk of Death within 180 Days after Beginning Therapy with Conventional as Compared with Atypical Antipsychotic Medications.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted analysis</td>
<td>1.51 (1.43–1.59)</td>
</tr>
<tr>
<td>Adjusted analysis†</td>
<td></td>
</tr>
<tr>
<td>Use of any conventional APM</td>
<td>1.37 (1.27–1.49)</td>
</tr>
<tr>
<td>Low dose of conventional APM (&lt;median)</td>
<td>1.14 (1.04–1.26)</td>
</tr>
<tr>
<td>High dose of conventional APM (&gt;median)</td>
<td>1.73 (1.57–1.90)</td>
</tr>
<tr>
<td>Adjusted analysis of death†</td>
<td></td>
</tr>
<tr>
<td>&lt;40 Days after beginning therapy</td>
<td>1.56 (1.37–1.78)</td>
</tr>
<tr>
<td>40–79 Days after beginning therapy</td>
<td>1.37 (1.19–1.59)</td>
</tr>
<tr>
<td>80–180 Days after beginning therapy</td>
<td>1.27 (1.14–1.41)</td>
</tr>
<tr>
<td>Adjusted analysis of patient subgroups†</td>
<td></td>
</tr>
<tr>
<td>With dementia</td>
<td>1.29 (1.15–1.45)</td>
</tr>
<tr>
<td>Without dementia</td>
<td>1.45 (1.30–1.63)</td>
</tr>
<tr>
<td>In a nursing home</td>
<td>1.26 (1.08–1.47)</td>
</tr>
<tr>
<td>Not in a nursing home</td>
<td>1.42 (1.29–1.56)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} APM denotes antipsychotic medication, and CI confidence interval.

\textsuperscript{†} Hazard ratios were adjusted for calendar year, age, sex, race, the presence or absence of cardiac arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, other ischemic heart disease, other cardiovascular disorders, cancer, HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, total number of medications used, hospitalizations, and nursing home stays.

![Figure 1. Rates of Death after the Initiation of Conventional and Atypical Antipsychotic Medications.](image)

*The rate of death before 10 days was not calculated, owing to insufficient data.*
sively involved patients with dementia, more data are needed on the absolute risk of death associated with atypical antipsychotic agents in elderly persons who do not have dementia. Our results suggest only that conventional antipsychotic medications do not appear to be safer than atypical agents in populations of elderly persons without dementia.

If confirmed, our results suggest that conventional antipsychotic medications should be included in the FDA's Public Health Advisory, which currently warns only of the increased risk of death with the use of atypical antipsychotic drugs in elderly persons who have dementia. Beyond arousing new concern about conventional agents, our data provide no guidance with regard to which pharmacologic or nonpharmacologic interventions should be used to manage the many conditions and symptoms for which antipsychotic medications are used.14 Traditionally, the benefits and risks of treatments in the elderly have simply been extrapolated from studies involving younger populations.9-12 As the recent FDA advisory and the results of this study show, such a practice can be misleading, given the unique needs and susceptibilities of older persons. Well-designed studies specifically involving the elderly are sorely needed to define optimal care.

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REFERENCES


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Messenger RNA for FOXP3 in the Urine of Renal-Allograft Recipients

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BACKGROUND

The outcome of renal transplantation after an episode of acute rejection is difficult to predict, even with an allograft biopsy.

METHODS

We studied urine specimens from 36 subjects with acute rejection, 18 subjects with chronic allograft nephropathy, and 29 subjects with normal biopsy results. Levels of messenger RNA (mRNA) for FOXP3, a specification and functional factor for regulatory T lymphocytes, and mRNA for CD25, CD3e, perforin, and 18S ribosomal RNA (rRNA) were measured with a kinetic, quantitative polymerase-chain-reaction assay. We examined associations of mRNA levels with acute rejection, rejection reversal, and graft failure.

RESULTS

The log-transformed mean (±SE) ratio of FOXP3 mRNA copies to 18S ribosomal RNA copies was higher in urine from the group with acute rejection (3.8±0.5) than in the group with chronic allograft nephropathy (1.3±0.7) or the group with normal biopsy results (1.6±0.4) (P<0.001 by the Kruskal–Wallis test). FOXP3 mRNA levels were inversely correlated with serum creatinine levels measured at the time of biopsy in the acute-rejection group (Spearman’s correlation coefficient =−0.38, P=0.02) but not in the group with chronic allograft nephropathy or the group with normal biopsy results. Analyses of receiver-operating-characteristic curves demonstrated that reversal of acute rejection can be predicted with 90 percent sensitivity and 73 percent specificity with use of the optimal identified cutoff for FOXP3 mRNA of 3.46 (P=0.001). FOXP3 mRNA levels identified subjects at risk for graft failure within six months after the incident episode of acute rejection (relative risk for the lowest third of FOXP3 mRNA levels, 6; P=0.02). None of the other mRNA levels were predictive of reversal of acute rejection or graft failure.

CONCLUSIONS

Measurement of FOXP3 mRNA in urine may offer a noninvasive means of improving the prediction of outcome of acute rejection of renal transplants.
Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD), but a shortage of organs limits its availability. Renal-allograft failure is the fourth most common cause of ESRD in the United States and contributes to the shortage of organs.

Acute rejection is an important risk factor for allograft failure. The current approach to treatment of acute rejection is uniform, although it is well recognized that some rejection episodes are not fully reversible and lead to long-term graft dysfunction and failure, whereas others are easily treatable and benign. The outcome of acute rejection is difficult to predict, and histologic features that are observed in allograft tissue obtained by core needle biopsy are currently the best predictors.

The invasive procedure of allograft biopsy, however, is associated with complications such as bleeding, arteriovenous fistula, and even graft loss. We previously reported a method using a quantitative polymerase chain reaction (PCR) to measure messenger RNA (mRNA) levels of immune products within urinary cells of renal-transplant recipients. This noninvasive and nucleic acid–based technique allows for the early diagnosis of acute rejection by detection of increased levels of cytolytic T-cell products such as granzyme B and perforin, integrins such as CD103, and key chemokine and chemokine-receptor combinations such as gamma-inducible protein of 10kD (IP-10) and its receptor, CXCR3, which promote effector T-cell recruitment to a transplant.

Recent studies have highlighted the role of a specialized subgroup of CD4+CD25+ T lymphocytes, termed regulatory T lymphocytes (Treg cells), in the suppression of autoimmunity. Treg cells specifically express the X-linked forkhead/winged helix transcription factor, FOXP3, and mutations in the human FOXP3 gene result in an autoimmune disease characterized by polyendocrinopathy and enteropathy that is fatal in infancy. In a similar manner, male mice with a loss-of-function mutation in the Foxp3 gene (scurfy mice) or with a deficiency of the Foxp3 gene generated by homologous recombination waste away and die within three to four weeks of life with multiorgan lymphocytic infiltrates; transfer of the Foxp3 gene reverses this process.

In view of the dominant role of Treg cells in the maintenance of self-tolerance and in view of the cells’ suppressive role in experimental models of transplantation tolerance, we reasoned that measurement of FOXP3 mRNA levels in urinary cells might provide insight into the immunologic events within a renal allograft undergoing acute rejection. We developed a kinetic, quantitative PCR assay and demonstrate that levels of FOXP3 mRNA in urinary cells predict the reversibility of acute rejection and identify patients at high risk for graft loss after an episode of acute rejection.

**Methods**

**Study cohorts**

We examined urine samples from 83 kidney-transplant recipients. In this group were 36 subjects with graft dysfunction (mean [±SD] creatinine level, 3.6±2.4 mg per deciliter [318.2±212.2 µmol per liter]) and biopsy-confirmed acute rejection (mean age, 41±12 years; 15 men and 21 women; 13 white, 12 black, and 11 with other racial or ethnic backgrounds; with 20 living and 16 deceased donors), 29 subjects with stable allograft function (mean creatinine level, 1.4±0.4 mg per deciliter [123.8±35.4 µmol per liter]) and normal allograft biopsy (mean age, 44±14 years; 15 men and 14 women; 12 white, 4 black, and 13 with other racial or ethnic backgrounds; with 26 living and 3 deceased donors), and 18 subjects with allograft dysfunction (mean creatinine level, 3.1±1.6 mg per deciliter [274.0±141.4 µmol per liter]) and biopsies classified as indicating chronic allograft nephropathy (mean age, 52±12 years; 9 men and 9 women; 9 white, 2 black, and 7 with other racial or ethnic backgrounds; with 5 living and 13 deceased donors).

Seventy-five of the 83 urine specimens were collected before the biopsy procedure, and 8 samples were obtained after the procedure. Formalin-fixed, paraffin-embedded renal-biopsy specimens were stained with hematoxylin and eosin, periodic acid–Schiff, and Masson’s trichrome stains and were scored with the use of the Banff’97 classification by a pathologist who was blinded to the results of molecular studies. Immunosuppression consisted of a calcineurin inhibitor–based regimen (cyclosporine or tacrolimus), with the administration of glucocorticoids, antilymphocyte antibodies (muromonab-CD3 [OKT3] or antithymocyte globulin), or both for the treatment of acute rejection. The study was approved by the institutional review board at the Weill Medical College of Cornell University in New York, and each patient gave written informed consent.
QUANTITATION OF mRNA BY KINETIC, QUANTITATIVE PCR

Total RNA was isolated from urine-cell pellets, quantified and reverse transcribed to complementary DNA (cDNA). We designed and synthesized oligonucleotide primers and fluorogenic probes for the measurement of mRNA levels of FOXP3, CD25, CD3\(\varepsilon\), perforin, and 18S ribosomal RNA (rRNA) (Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). PCR analysis was performed by a two-step process, a preamplification step followed by measurement of mRNA with an ABI Prism 7700 system (the PCR protocol is provided in the Supplementary Appendix). Transcript levels were calculated by a standard curve method, and mRNA copy numbers were normalized with the use of 18S rRNA copy numbers (the number of mRNA copies in 1 µg of RNA divided by the number of 18S rRNA copies in 1 fg of RNA). When no detectable level of a transcript was found, a value equal to half the minimum observed level was assigned. For an estimation of group means, this method is considered a reasonable substitute for the value of zero or the minimum detected value; moreover, the nonparametric statistical tests of group differences reported below are not affected by the choice of value.

STATISTICAL ANALYSIS

The levels of mRNA for FOXP3, CD25, CD3\(\varepsilon\), perforin, and 18S rRNA deviated from a normal distribution (P<0.001), but a log transformation substantially reduced the positive skew. We used the 18S-normalized level as the dependent variable in a Kruskal–Wallis test to identify any differences among the group with acute rejection, the group with chronic allograft nephropathy, and the group with normal biopsy results and was higher than the levels in both the 18 subjects with chronic allograft nephropathy (1.3±0.7) and the 29 subjects with normal biopsy results (1.6±0.4, P<0.001 by the Kruskal–Wallis test) (Fig. 1A). Among the three groups, the 18S-normalized, log-transformed mRNA levels of CD25 (6.9±0.4, 4.0±0.5, and 2.8±0.6, respectively; P<0.001), CD3\(\varepsilon\) (8.2±0.4, 4.3±0.5, and 1.6±0.5; P<0.001), and perforin (7.6±0.4, 4.5±0.4, and 2.8±0.4; P<0.001) were also highest in the acute-rejection cohort (Fig. 1B, 1C, and 1D).

FOXP3 mRNA LEVELS AND DISEASE SEVERITY

We observed a significant inverse relationship between the levels of FOXP3 mRNA and serum creatinine measured during an episode of acute rejection (Spearman’s correlation coefficient [\(r_s\)] = −0.38, P = 0.02). By contrast, serum creatinine levels were not significantly related to mRNA levels of CD25 (\(r_s\) = −0.01, P = 0.93), CD3\(\varepsilon\) (\(r_s\) = −0.11, P = 0.54), or perforin (\(r_s\) = −0.23, P = 0.18) in the acute-rejection group. Also, the mean (±SE) serum creatinine level in the 16 subjects with acute rejection of Banff grade IA (moderate tubulitis) did not differ significantly from that of the 20 subjects with grade IB (severe tubulitis) or more (3.3±0.6 mg per deciliter [291.7±53.0 µmol per liter] as compared with 3.8±0.6 mg per deciliter [318.2±53.0 µmol per liter], P = 0.57).

There was no correlation between the levels of FOXP3 mRNA and serum creatinine that were measured in the group with chronic allograft nephropathy (\(r_s\) = 0.02, P = 0.93) or the group with normal biopsy results (\(r_s\) = −0.08, P = 0.67).

FOXP3 mRNA LEVELS AND REVERSAL OF ACUTE REJECTION

Twenty-six of the 36 episodes of acute rejection qualified as successfully reversed; the remaining 10 did...
not. Levels of FOXP3 mRNA in urinary cells were significantly higher in the group with successful reversal than in the group without reversal (mean ±SE level, 4.7±0.5 and 1.5±0.7, respectively; P = 0.001) (Fig. 2A). In the two groups, the levels of mRNA for CD25 (7.3±0.4 and 6.0±0.9, P = 0.22), CD3e (8.5±0.5 and 7.4±0.8, P = 0.35), and perforin (7.8±0.5 and 7.3±0.7, P = 0.43) were not informative of outcome (Fig. 2B, 2C, and 2D).

The ROC curves (Fig. 3) show the fraction of true positive results (sensitivity) and false positive results (1−specificity) for various cutoff levels of mRNA for FOXP3, CD25, CD3e, and perforin. The log-transformed threshold that gave the maximal sensitivity and specificity for FOXP3 mRNA was 3.46; using the cutoff value of 3.46 derived from the data, the FOXP3 mRNA level predicted rejection reversal with a sensitivity of 90 percent and a specificity of 73 percent (P = 0.001) (Fig. 3A). The levels of mRNA for CD25, CD3e, and perforin were not predictive of reversal of acute rejection (Fig. 3B, 3C, and 3D).
Successful reversal of acute rejection, as compared with unsuccessful reversal, was not predicted by the subjects’ age (mean [±SD], 41±2.2 years and 40±4.6 years, respectively; P=0.68), sex (10 men and 16 women vs. 5 men and 5 women, P=0.71), race (10 white, 6 black, and 10 with other race or ethnic background vs. 3 white, 6 black, and 1 with other race or ethnic background; P=0.08), graft-donor source (15 living and 11 deceased vs. 5 living and 5 deceased, P=0.68), Banff histologic grade (11 with IA and 15 with >IA vs. 5 with IA and 5 with >IA, P=0.68), or initial antirejection treatment (24 with glucocorticoids and 2 with antilymphocyte antibodies vs. 7 with glucocorticoids and 3 with antilymphocyte antibodies, P=0.12). Among subjects with successful reversal, as compared with those with unsuccessful reversal, serum creatinine levels (median levels, 2.3 mg per deciliter and 6.5 mg per deciliter, respectively; P<0.001) and the time from kidney transplantation to the development of acute rejection (median time, 82 days and 523 days, respectively; P=0.008) were lower. In logistic-regression analyses predicting nonresponse, levels of \textit{FOXP3} mRNA in urinary cells remained significant after statistical control for serum creatinine level (P=0.04) and the time from transplantation to rejection (P=0.02).

A linear combination of levels of \textit{FOXP3} mRNA and creatinine was a better predictor of rejection reversal (90 percent sensitivity and 96 percent specificity) than \textit{FOXP3} mRNA levels alone (90 percent sensitivity and 73 percent specificity) or serum creatinine levels alone (85 percent sensitivity and 90 percent specificity).
Messenger RNA for FOXP3 in the Urine of Renal-Allograft Recipients

Ten of the 36 subjects with acute rejection lost their grafts within six months after the incident episode of acute rejection, and 9 of those 10 subjects did not respond to the initial antirejection therapy. Renal-allograft recipients with a failed allograft within six months after the episode of acute rejection had significantly lower FOXP3 mRNA levels in their urinary cells than the 26 subjects who had a functioning allograft (2.0±0.8 and 4.5±0.5, respectively; P=0.01). In the two groups, the levels of mRNA for CD25 (6.6±0.7 and 7.1±0.5, P=0.33), CD3ε (7.9±0.7 and 8.3±0.5, P=0.76), and perforin (7.8±0.6 and 7.6±0.5, P=0.90) did not predict allograft loss.

The rate of and relative risk of graft failure within six months after an episode of acute rejection, for thirds of each mRNA measure, are shown in Figure 4. At the highest third of FOXP3 mRNA levels, the graft failure rate was 8 percent; at the middle third, the graft failure rate was 25 percent and the relative risk was 3; and at the lowest third, the graft failure rate was 50 percent and the relative risk was 6 (P=0.02 by the chi-square test for linear trend) (Fig. 4A). In contrast, the rate of graft failure after an episode of acute rejection did not differ significantly across the thirds of mRNA levels for CD25, CD3ε, and perforin (Fig. 4B, 4C, and 4D).

Graft failure as compared with graft success was not predicted by the subjects’ age (mean ±SD ages, 39±4.2 years and 42±2.4 years, respectively; P=0.52), sex (4 men and 6 women vs. 11 men and 15 women, P=0.90), race (3 white, 6 black, and 1 with other race or ethnic background vs. 10 white, 6 black, and 10 with other race or ethnic back-
ground; P = 0.08), graft-donor source (5 living and 5 deceased vs. 15 living and 11 deceased, P = 0.68), Banff histologic grade (5 with IA and 5 with >IA vs. 11 with IA and 15 with >IA, P = 0.68), or initial anti-rejection treatment (24 with glucocorticoids and 2 with antilymphocyte antibodies vs. 7 with glucocorticoids and 3 with antilymphocyte antibodies, P = 0.12). In subjects with graft failure, as compared with subjects with graft success, serum creatinine levels (median levels, 6.5 mg per deciliter [574.6 µmol per liter] and 2.3 mg per deciliter [203.3 µmol per liter], respectively; P < 0.001) and the time from kidney transplantation to the development of acute rejection (median time, 562 days and 82 days; P = 0.003) were significantly greater. In a logistic-regression analysis, FOXP3 mRNA levels became nonsignificant after control for serum creatinine levels (P = 0.13) or time between transplantation and rejection (P = 0.09).

A linear combination of levels of FOXP3 mRNA and creatinine was a better predictor of graft failure (90 percent sensitivity and 92 percent specificity) than were either FOXP3 mRNA levels alone (80 percent sensitivity and 69 percent specificity) or serum creatinine levels alone (85 percent sensitivity and 90 percent specificity).

**FOXP3 mRNA Levels and Time to Acute Rejection**

Late acute rejection (acute rejection occurring at least three months after transplantation) results in an outcome that is inferior to that of early acute rejection.26,27 We found a strong inverse relationship between levels of FOXP3 mRNA in urinary cells and the time from kidney transplantation to the development of acute rejection (r = −0.42, P = 0.01) (Fig. 5A). Levels of FOXP3 mRNA in urinary cells were lower in 11 urine specimens from patients with late acute rejection than in 25 specimens from patients with early acute rejection (mean [±SE] lev-
el, 2.5±0.6 and 4.7±0.5; P=0.009). CD25 mRNA levels also showed an inverse relation (r_s=−0.45, P=0.006) (Fig. 5B), and the levels were lower during late rejection than during early acute rejection (5.8±0.8 and 7.4±0.4, P=0.07). There was no inverse relation between the time from kidney transplantation to the development of acute rejection and the mRNA levels of CD3ε (r_s=−0.26, P=0.12) (Fig. 5C) or perforin (r_s=−0.02, P=0.91) (Fig. 5D). There was also no correlation between the serum creatinine levels at the time of acute rejection and the time from kidney transplantation to the development of acute rejection (r_s=0.23, P=0.17).

**Discussion**

Previous studies have associated acute allograft rejection with cytotoxic T cells and have shown that monitoring the levels of these cells in blood, urine, or both is helpful in the treatment of renal-allograft recipients. Our study suggests that levels of FOXP3 mRNA in urinary cells may serve as a mechanistically informative biomarker of acute-rejection outcome.

Depletion or dysfunction of Treg cells can result in autoimmune disease; tolerance to experimental allografts, on the other hand, is associated with graft infiltration by Treg cells. An attractive hypothesis is that the Treg cells prevent the emergence of effector T cells, and that the absence of disease or tolerance is due to the lack of an immune response. An alternative hypothesis is that Treg cells play a “damage control” role rather than a preventive one. We suggest that the host allograft and the host mutual immunity repertoire during acute rejection includes the activation of graft-destructive effector cells as well as graft-protective Treg cells. We observed that levels of FOXP3 mRNA in urinary cells, a defining functional marker of Treg cells, and mRNA for perforin, a cytotoxic effector, are both expressed in a heightened fashion during acute rejection and that high levels of FOXP3 mRNA are associated with reversible acute rejection and a lower risk of graft failure. These findings are consistent with the hypothesis that Treg cells serve to limit allograft immunity and that the lack of counterregulation by Treg cells during an episode of acute rejection results in unrestrained effector-cell activity, impaired allograft function, and even graft failure.

Histologic analysis of renal allografts is considered to be the best predictor of acute rejection. However, it has long been recognized that cellular interstitial infiltration is not invariably associated with allograft dysfunction or failure. In the current study, Banff grades of acute rejection did not predict rejection outcome, and the serum creatinine levels did not vary across Banff grades. We suggest that graft-infiltrating cells comprise both graft-destructive cells such as cytotoxic T cells and graft-protective FOXP3-expressing Treg cells and that graft dysfunction and response to therapy may be predicted more accurately when the heterogeneous nature of the cellular components is better resolved.

Elevated levels of serum creatinine are an established risk factor for renal allograft failure and in our studies were shown to be a strong predictor of the outcome of acute rejection. Do levels of FOXP3 mRNA in urinary cells provide information above and beyond that provided by serum creatinine levels? In our study, levels of serum creatinine and FOXP3 mRNA in urinary cells were independent predictors of reversal of acute rejection. Moreover, rejection reversal and graft loss were predicted with a higher degree of accuracy with the use of levels of both FOXP3 mRNA and creatinine than with either one alone. However, since our estimates of sensitivity and specificity were calculated from the same sample that was used to select the cutoff points, the estimates are upwardly biased and need to be reevaluated in an independent sample.

In both adult and pediatric recipients of renal allografts, an episode of late acute rejection is associated with a lower rate of graft survival than an episode of early acute rejection. Our finding of an inverse relationship between levels of FOXP3 mRNA in urinary cells and the time to acute rejection suggests a cellular mechanism for the hitherto unexplained poor outcome associated with late acute rejection.

A mechanistic hypothesis engendered by our study is that drugs that enhance the generation of Treg cells, or the administration of Treg cells themselves, may improve the outcome of acute rejection. Cyclosporine and tacrolimus both inhibit the production of interleukin-2, an essential growth factor for Treg cells, but induce the production of transforming growth factor β1, an inducer of FOXP3 and a promoter of the development of CD4+CD25+ Treg cells. Sirolimus (rapamycin) has been shown to promote the expansion of murine Treg cells in vitro, and glucocorticoids have been reported to increase the expression of FOXP3 mRNA in human CD4+ cells. However, the in vivo effects...
of drugs on the induction, expansion, and function of Treg cells in allograft recipients remain to be fully characterized.

How might FOXP3-expressing Treg cells exert their salutary activity during an episode of acute rejection? Treg cells have been shown to dampen or suppress local host immune responses by acting on antigen-presenting cells, directly modulating effector-cell functions, or both.\(^\text{14,15}\) Mechanisms of immunosuppression by FOXP3-expressing Treg cells include direct cell contact, cytokine signaling, and inhibition of transcription of genes central to effector functions.\(^\text{40}\) The role of these mechanisms in mitigating the acute-rejection response remains undetermined.

In sum, our study suggests that levels of FOXP3 mRNA in urinary cells may serve as a mechanistically informative biomarker of acute-rejection outcome, with lower levels associated with irreversible acute rejection and even graft failure. In addition to suggesting a robust cellular mechanism for the clinically important differences in the outcome of acute-rejection episodes, the strategy we present here may ultimately lead to individualized treatment of renal-allograft recipients and inform antirejection therapy, including the consideration of infusion of Treg cells to treat acute rejection of allografts.

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A U.S. patent entitled “Methods of Evaluating Transplant Rejection” (6187534) was issued on February 13, 2001; Dr. Suthanthiran is one of the inventors. The patent is owned jointly by Harvard Medical School, Cornell University, and the Beth Israel–Deaconess Medical Center, Boston.

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REFERENCES


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Fatal Toxic Shock Syndrome Associated with Clostridium sordellii after Medical Abortion


From the Centers for Disease Control and Prevention, Atlanta (M.F., J.B., J.G., S.R., W.J.S., S.R.Z.); the California Emerging Infections Program, Richmond (J.K.H.); the Alameda County Coroner's Office (S.H.V.M.) and Health Department (A.J.), Oakland, Calif.; the Department of the Coroner (V.P., D.B.W.) and the Department of Health Services (D.E.D.), Los Angeles; and the Orange County Health Care Agency, Santa Clara, Calif. (M.C.). Address reprint requests to Dr. Fischer at the Centers for Disease Control and Prevention, P.O. Box 2087, Mailstop P-02, Fort Collins, CO 80522, or at mfischer@cdc.gov.


Endometritis and toxic shock syndrome associated with Clostridium sordellii have previously been reported after childbirth and, in one case, after medical abortion. We describe four deaths due to endometritis and toxic shock syndrome associated with C. sordellii that occurred within one week after medically induced abortions. Clinical findings included tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. These cases indicate the need for physician awareness of this syndrome and for further study of its association with medical abortion.

Clostridium sordellii is a gram-positive anaerobic bacillus that has been reported as a cause of infection in the female genital tract and fatal toxic shock syndrome. Of 10 cases identified in the literature, 8 occurred after delivery of live-born infants,1–6 1 occurred after a medical abortion,7 and 1 was not associated with pregnancy.8 We report four additional deaths due to C. sordelli toxic shock syndrome that occurred among previously healthy women after abortions that were medically induced with 200 mg of oral mifepristone and 800 µg of vaginal misoprostol.

Case Reports

Patient 1

Patient 1 was a previously healthy 18-year-old woman who underwent a medically induced abortion at 47 days of gestation by means of 200 mg of oral mifepristone followed by 800 µg of vaginal misoprostol. Four days after receiving mifepristone, the patient presented to an emergency department with reports of abdominal cramping and dysuria. She had taken acetaminophen with codeine after the abortion. On physical examination, she was afebrile with normal vital signs and no abdominal tenderness. Pelvic examination revealed no uterine tenderness or adnexal mass. No laboratory studies or cultures were performed. She received hydromorphone and promethazine and was discharged taking acetaminophen and codeine.

The patient returned three days later and reported nausea, vomiting, and weakness. On admission, she was afebrile (temperature, 36.3°C), tachyycardic (heart rate, 147 beats per minute), and hypotensive (blood pressure, 78/53 mm Hg) and had dry mucous membranes but unremarkable findings on abdominal and pelvic examinations. Laboratory studies showed an elevated white-cell count of 45,600 cells per microliter, a platelet count of 387,000 cells per microliter, and a hematocrit of 52 percent. Creatinine and liver-function studies were normal. Blood cultures obtained before antibacterial thera-
Brief Report

Py were later found to be negative for bacteria; vaginal cultures grew Gardnerella species. Ultrasonographic examination of the pelvis showed a residual gestational sac in the uterus and a large amount of free peritoneal fluid. A chest radiograph showed bilateral interstitial infiltrates.

Initial treatment included supplemental oxygen, intravenous fluids, and antibacterial therapy with vancomycin and piperacillin–tazobactam. During the next few hours, the patient had respiratory distress and hypotension requiring mechanical ventilation and vasopressor support. Initial arterial blood gas measurements revealed severe metabolic acidosis, with a pH of 7.15, a partial pressure of carbon dioxide of 36 mm Hg, and a bicarbonate concentration of 13 mmol per liter. Within seven hours after admission, the white-cell count increased to 107,000 cells per microliter, with a hematocrit of 58 percent and a platelet count of 158,000 cells per microliter. Urine output and the serum albumin concentration decreased markedly, but concentrations of hepatic enzymes, bilirubin, and creatinine remained normal. Refractory bradycardia, hypotension, and hypoxemia developed, and the patient died approximately 10 hours after admission.

Patient 2

Patient 2 was a previously healthy 21-year-old woman who underwent a medically induced abortion at 43 days of gestation by means of 200 mg of oral mifepristone followed by 800 µg of vaginal misoprostol. Five days after receiving mifepristone, she presented to a local emergency department reporting nausea, vomiting, diarrhea, and severe abdominal pain. The patient was afebrile (temperature, 36.2°C), with a heart rate of 104 beats per minute and blood pressure of 115/76 mm Hg. Physical examination was unremarkable except for moderate abdominal tenderness. Laboratory findings included a white-cell count of 21,800 cells per microliter, a platelet count of 256,000 cells per microliter, and a hematocrit of 40 percent. Ultrasonographic examination of the pelvis showed a left adnexal mass and fluid in the cul-de-sac. The patient received intravenous fluids, promethazine, and morphine and was admitted to the hospital to rule out an ectopic pregnancy.

The following day, persistent tachycardia (heart rate, 130 to 140 beats per minute), hypotension (blood pressure, 80/40 mm Hg), lethargy, decreased urine output, and diffuse abdominal tenderness developed, and the patient was transferred to the intensive care unit. Laboratory findings included a white-cell count of 120,200 cells per microliter, a platelet count of 91,000 cells per microliter, a hematocrit of 45 percent, a creatinine concentration of 1.9 µg per deciliter (168 µmol per liter), an albumin concentration of 1.0 g per deciliter, and a prothrombin time of 18.3 seconds with normal levels of aminotransferases and bilirubin. Arterial blood gas measurements showed severe metabolic acidosis, with a pH of 7.15, a partial pressure of carbon dioxide of 29 mm Hg, and a bicarbonate concentration of 10 mmol per liter. Antibacterial therapy was initiated with piperacillin–tazobactam and metronidazole; blood cultures obtained before antibacterial therapy were subsequently found to be negative for bacteria. Within three hours after being transferred to the intensive care unit, the patient had a cardiopulmonary arrest requiring mechanical ventilation and vasopressor support. Emergency laparotomy showed generalized edema of the abdominal and pelvic organs and 1000 ml of serous peritoneal fluid. Gram’s stain and aerobic and anaerobic cultures of peritoneal fluid obtained intraoperatively were negative for bacteria. The patient died during the surgical procedure, approximately 23 hours after her initial presentation to the hospital.

Patient 3

Patient 3 was a previously healthy 22-year-old woman who underwent a medically induced abortion at 53 days of gestation by means of 200 mg of oral mifepristone followed by 800 µg of vaginal misoprostol. Five days after receiving mifepristone, she reported abdominal pain and vomiting. The following morning she became unresponsive. When paramedics arrived, she had no spontaneous respirations or cardiac activity. She was transported to a local emergency department while receiving ongoing cardiopulmonary resuscitation. Physical examination showed a rectal temperature of 38.9°C, fixed and dilated pupils, and mild abdominal distention. The serum glucose concentration was 108 mg per deciliter. Toxicologic evaluation was negative. No other laboratory studies or cultures were performed. The patient was intubated and received intravenous fluids, epinephrine, and atropine. Resuscitation efforts were discontinued 40 minutes after her arrival at the emergency department.

Patient 4

Patient 4 was a previously healthy 34-year-old woman who underwent a medically induced abortion at
45 days of gestation by means of 200 mg of oral mifepristone followed by 800 µg of vaginal misoprostol. Four days after receiving mifepristone, she presented to a local emergency department reporting nausea, vomiting, and severe abdominal pain. She had taken ondansetron and acetaminophen with hydrocodone after the abortion. The patient was afebrile (temperature, 36.3°C), with a heart rate of 89 beats per minute and blood pressure of 99/63 mm Hg. Physical examination was unremarkable except for moderate abdominal tenderness. Laboratory findings included a white-cell count of 55,400 cells per microliter, a platelet count of 149,000 cells per microliter, and a hematocrit of 59 percent. Ultrasonographic examination of the pelvis showed an empty uterus. Initial treatment included intravenous fluids, ondansetron, and hydromorphone.

After the patient received 2 liters of normal saline, a repeated blood count showed a white-cell count of 87,600 cells per microliter, a platelet count of 63,000 cells per microliter, and a hematocrit of 61 percent. Serum chemical analyses including liver-function tests were unremarkable. Aerobic and anaerobic blood cultures and a urine culture were obtained but were subsequently negative for bacteria; antibacterial therapy was initiated with piperacillin–tazobactam and metronidazole. A chest radiograph was normal. Computed tomography of the abdomen showed only a moderate volume of free fluid. Although the patient received 5 liters of intravenous fluids, worsening tachycardia and hypotension with minimal urine output developed. Arterial blood gas measurements showed severe metabolic acidosis, with a pH of 7.07, a partial pressure of carbon dioxide of 10 mm Hg, and a bicarbonate concentration of 3 mmol per liter. Further therapy included sodium bicarbonate and vasopressor support, but refractory hypotension developed and the patient died approximately 12 hours after presentation.

We reviewed medical and autopsy records for each patient. Formalin-fixed tissues were evaluated at the Centers for Disease Control and Prevention. Immunohistochemical assays were performed for clostridium species, *Staphylococcus aureus*, group A streptococcus, and neisseria species by means of a two-step indirect staining technique with immunoalkaline phosphatase. The polyclonal anti-clostridium antibody used in the immunohistochemical assay cross-reacts with multiple clostridium species.9 DNA was extracted from formalin-fixed uterine tissue with the use of the QIAamp DNA Mini Kit (Qiagen) and was evaluated with broad-range and *C. sordellii*–specific polymerase-chain-reaction (PCR) assays targeting the 16S ribosomal RNA (rRNA) gene and with PCR assays targeting the *C. sordellii* cytotoxin L and phospholipase C genes (Table 1).10-14 Amplified PCR products were directly sequenced and, with the use of the Basic Local Methods

<table>
<thead>
<tr>
<th>Gene Target</th>
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</tr>
</tbody>
</table>

* A broad-range PCR assay was used to target the 16S rRNA gene.
† A *C. sordellii*–specific PCR assay was used to target the 16S rRNA gene.
‡ CytL denotes the cytotoxin L–encoding gene of *C. sordellii*.
§ Primers were designed for this investigation from the published sequence of *C. sordellii* (GenBank accession number X82638).13
¶ Csp denotes the phospholipase C gene of *C. sordellii*.
¿ Primers were designed for this investigation from the published sequence of *C. sordellii* (GenBank accession number AB061868).14
Alignment Search Tool (BLAST), compared with sequences available in the GenBank database.

The National Center for Infectious Diseases determined that this investigation was defined as a public health response. Approval of the institutional review boards and consent of the next of kin were not required to evaluate and publish these case reports.

RESULTS

Autopsy of Patient 1 revealed marked pleural, pericardial, and peritoneal effusions. Histopathological examination of the uterus showed inflammation of endometrium and myometrium, multiple small abscesses, necrosis, and hemorrhage (Fig. 1A). There was no retained fetal or placental tissue. Other organs were unremarkable. Mixed bacteria, including numerous gram-positive bacilli, were seen in the endometrium (Fig. 1B). Postmortem cultures were not performed. Immunohistochemical testing of uterine tissue was negative for S. aureus, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation in the endometrium and myometrium (Fig. 1C). Clostridial antigens were noted in blood vessels of the uterus (Fig. 1D) but were not observed in brain, heart, lung, liver, kidney, or adrenal tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with C. sordellii. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed

Figure 1. Photomicrographs of the Uterine Tissue of Patient 1.
Panel A shows hemorrhage, inflammation, and necrosis of the endometrium (hematoxylin and eosin). Abundant gram-positive bacilli were observed in the necrotic endometrial tissue (Panel B, Gram’s stain). Clostridial antigens (red staining) were seen inside inflammatory cells present in the necrotic endometrial tissue (Panel C, immunohistochemical assay with the use of polyclonal anti–clostridium species antibody) and inside myometrial blood vessels closest to the necrotic endometrium (Panel D, immunohistochemical assay with the use of polyclonal anti–clostridium species antibody).
of uterine tissue was negative for the endometrium. Immunohistochemical testing predominantly gram-positive bacilli, were seen in retained necrotic decidual tissue. Mixed bacteria, predominantly gram-positive bacilli, were seen in the endometrium. Immunohistochemical testing of uterine tissue was negative for S. aureus, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed staining of bacilli and abundant granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, spleen, pancreas, kidney, adrenal, or ovarian tissues. The 16S rRNA gene sequences amplified from the uterus showed 98 percent identity with C. sordellii. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 98 percent and 97 percent identity with C. sordellii, respectively.

Autopsy of Patient 3 revealed pleural and peritoneal effusions. Histopathological examination of the uterus showed extensive inflammation, abscess formation, edema, necrosis, and hemorrhage. There was no retained fetal or placental tissue and no evidence of ectopic pregnancy. Mixed bacteria, including numerous gram-positive bacilli, were seen in the endometrium. Postmortem cultures were not obtained. Immunohistochemical testing of uterine tissue was negative for group A streptococcus and neisseria species but showed S. aureus antigens on the endometrial surface. Clostridium immunohistochemical analysis showed extensive staining of bacilli and granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, or kidney tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 97 percent identity with C. sordellii. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 99 percent and 98 percent identity with C. sordellii, respectively.

Autopsy of Patient 4 revealed pleural, pericardial, and peritoneal effusions. Histopathological examination of the uterus showed severe inflammation of endometrium and myometrium, necrosis, and hemorrhage, with extensive inflammation and edema. Abundant gram-positive bacilli were seen in the endometrium. Postmortem cultures of the endometrium grew Escherichia coli and an anaerobic gram-positive bacillus that was discarded before further identification. Immunohistochemical testing of uterine tissue was negative for S. aureus, group A streptococcus, and neisseria species. Clostridium immunohistochemical analysis showed staining of bacilli and abundant granular antigens associated with areas of inflammation throughout the endometrium and myometrium. Clostridial antigens were not observed in heart, lung, liver, spleen, pancreas, kidney, adrenal, or ovarian tissues. The 16S rRNA gene sequences amplified from uterine tissue showed 98 percent identity with C. sordellii. Cytotoxin L and phospholipase C gene sequences amplified from the uterus showed 98 percent and 97 percent identity with C. sordellii, respectively.

**Discussion**

We describe four deaths associated with C. sordellii endometritis and toxic shock syndrome that occurred within one week after medically induced abortions. The clinical and pathological findings in these cases are similar to those in 10 other cases of C. sordellii infection of the genital tract reported in the literature. Of the 10 previous cases that we identified, all occurred in previously healthy young women, and 9 occurred within one week after delivery (8 women) or after abortion (1 woman). Notable clinical features included absence of fever and rash, dramatic leukemoid reaction, capillary leak and fluid sequestration with associated hemoconcentration, refractory tachycardia and hypotension, and marked edema of infected tissues without gas production or extensive myonecrosis. All the cases had a fulminant course and fatal outcome. Eight of the previously reported cases had evidence of a polymicrobial infection. Although infections of the female genital tract often include mixed bacteria, the role of other organisms in toxic shock syndrome associated with C. sordellii is unclear.

C. sordellii is an infrequent human pathogen but has been reported as a cause of pneumonia, endocarditis, arthritis, peritonitis, and myonecrosis. C. sordellii bacteremia and sepsis occur rarely, primarily among patients with serious underlying conditions. Fulminant toxic shock syndrome among previously healthy persons has been described in only a small proportion of cases of C. sordellii infection, most often those associated
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Currently Reported Patients (N=4)</th>
<th>Previously Reported Patients (N=10)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age —— yr</strong></td>
<td>Median 22</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td>18–34</td>
<td>23–40</td>
</tr>
<tr>
<td><strong>Fatal outcome — no. (%)</strong></td>
<td>4 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td><strong>Underlying medical conditions — no.</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Preceding event — no. (%)</strong></td>
<td>8 (80)†</td>
<td>1 (10)</td>
</tr>
<tr>
<td><strong>Time course (days)</strong></td>
<td>4–5</td>
<td>2–5</td>
</tr>
<tr>
<td>From event to onset of symptoms</td>
<td>Median 5</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>4–5</td>
<td>2–5</td>
</tr>
<tr>
<td>From hospitalization to death</td>
<td>Median 0</td>
<td>0</td>
</tr>
<tr>
<td>Range</td>
<td>0–1</td>
<td>0–3</td>
</tr>
<tr>
<td><strong>Clinical signs and symptoms — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature &gt;38.0°C</td>
<td>1 (25)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>4 (100)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Pleural or peritoneal effusions</td>
<td>3 (75)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Vomiting or diarrhea</td>
<td>4 (100)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (100)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (10)‡</td>
</tr>
<tr>
<td><strong>Laboratory findings — no. (%)</strong></td>
<td>3 (75)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>White-cell count &gt;50,000 cells/microliter</td>
<td>3 (75)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Hematocrit ≥50%</td>
<td>3 (75)</td>
<td>7 (70)</td>
</tr>
<tr>
<td><strong>Microbiologic findings — no. (%)</strong></td>
<td>4 (100)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Evidence of polymicrobial infection</td>
<td>4 (100)</td>
<td>8 (80)</td>
</tr>
<tr>
<td><strong>C. sordellii isolated from blood</strong></td>
<td>0</td>
<td>1 (10)</td>
</tr>
<tr>
<td><strong>Focus of infection — no. (%)</strong></td>
<td>4 (100)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Uterus</td>
<td>4 (100)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Site of episiotomy</td>
<td>0</td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>Pathological findings at the focus of infection — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>3 (75)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>4 (100)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Acute inflammation</td>
<td>4 (100)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3 (75)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Gas</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* This information has been reported elsewhere.1–6
† Six deliveries were vaginal, and two were by cesarean section.1–6
‡ This rash was described as vesicles on the perineum that enlarged to bullous lesions and spread to the legs and trunk.6
with gynecologic infections and neonatal omphalitis.\(^1\)\(^-\)\(^8\),\(^17\) The distinctive clinical manifestations of \(C.\) \(sordellii\) toxic shock syndrome result from the production of specific exotoxins, as do those of other illnesses caused by clostridium species.\(^15\),\(^16\),\(^19\)

In animal models, \(C.\) \(sordellii\) lethal toxin causes findings similar to those described in these human cases.\(^15\),\(^19\) Lethal toxin is expressed variably by different \(C.\) \(sordellii\) strains,\(^20\) and its cytopathic effects are markedly enhanced by a low pH.\(^21\)

Although \(C.\) \(sordellii\) has rarely been identified in the genital tract, other clostridium species colonize the vagina in 4 percent to 18 percent of healthy women and commonly are associated with postpartum endometritis and septic abortion.\(^22\)-\(^25\) Vaginal flora vary with age, sexual activity, menstrual cycle, pregnancy, medications, and surgery,\(^22\) and the apparent association between \(C.\) \(sordellii\) toxic shock syndrome and gynecologic infections may be attributed to a rare confluence of events. Pregnancy, childbirth, or abortion may predispose a small number of women to acquire \(C.\) \(sordellii\) in the vaginal tract, with dilatation of the cervix allowing for ascending infection of necrotic decidual tissue. Furthermore, the acidic pH of the vaginal tract may enhance the cytopathic effects of \(C.\) \(sordellii\) lethal toxin and further potentiate systemic illness.

The fastidious anaerobic growth, variable staining characteristics, and complex biochemical profiles of clostridium species make them difficult to isolate and identify, and additional cases of \(C.\) \(sordellii\) infection of the genital tract in which the organism was not cultured, speciated, or reported probably exist.\(^26\),\(^27\) In the four cases reported here, evidence of \(C.\) \(sordellii\) infection was established with the use of anti–clostridium species immunohistochemical assay and both organism-specific and broad-range PCR assays performed on fixed uterine tissue. Identification of additional cases and application of anaerobic culture techniques or new diagnostic approaches are needed to define the true burden of \(C.\) \(sordellii\) in gynecologic infections.

There are limited data regarding the optimal therapy for \(C.\) \(sordellii\) toxic shock syndrome. As with other severe histotoxic clostridial infections, aggressive surgical wound débridement, removal of infected organs (e.g., by means of hysterectomy), and antibacterial agents with good anaerobic activity are logical first steps to decrease the bacterial load and minimize further production of toxins.\(^1\)-\(^23\) In vitro susceptibility testing on 24 \(C.\) \(sordellii\) strains showed low minimal inhibitory concentrations for penicillin, ampicillin, erythromycin, rifampin, tetracycline, cefoxitin, clindamycin, and metronidazole;\(^28\) antibiotics that interfere with bacterial protein synthesis (such as clindamycin) may have additional benefit. However, débridement, surgery, and antibacterial therapy will not mitigate the effects of preformed toxin. There are no clinical data on the use of immunoglobulin or anti–lethal toxin antibodies for treatment of \(C.\) \(sordellii\) infections.\(^16\),\(^17\)

These cases demonstrate that serious infection can occur after medically induced abortion, much as it can occur after childbirth, spontaneous abortion, and surgical abortion. However, available data suggest that the risk of such infection is low.\(^29\),\(^30\) In 2000, 600 mg of oral mifepristone plus 400 \(\mu\)g of oral misoprostol was approved for use in the United States to medically terminate a pregnancy of up to seven weeks’ gestation. As of July 2005, five deaths that occurred after medically induced abortions had been reported to the Food and Drug Administration (FDA). These include the four patients described here and one patient whose death was attributed to a ruptured ectopic pregnancy.\(^31\) Since its approval, there have been an estimated 460,000 uses of mifepristone plus misoprostol in the United States.\(^32\) It is not clear how many women this estimate represents. The 460,000 uses may include the regimen approved by the FDA or other dosages, such as 200 mg of oral mifepristone followed by 800 \(\mu\)g of intravaginal misoprostol.

There are no available incidence data for pregnancy-related \(C.\) \(sordellii\) infections or toxic shock syndrome. However, overall rates of infection-related deaths after pregnancy are well described. From 1991 to 1999, 259 maternal deaths due to infection were identified after 35,701,875 live births in the United States.\(^33\),\(^34\) From 1981 to 1991, 37 infection-related maternal deaths were associated with 9,279,100 spontaneous abortions at less than 20 weeks’ gestation.\(^35\) From 1988 to 1997, 25 maternal deaths attributed to infection were reported after 13,161,608 surgical abortions at any point in gestation.\(^36\) These data must be interpreted with caution, however, because each estimate was obtained with the use of different methods and over different periods. Furthermore, the risk of maternal death after surgical abortion increases with gestational age, and there are no published estimates for the rate of maternal death after surgical abortion performed during the first trimester.

In 2001, one additional death due to \(C.\) \(sordellii\)
infection after medical abortion was reported in Canada. Although all four cases reported in the present study occurred in California, there were no epidemiologic links identified between the patients, and the medications received were from different lots. Some researchers have speculated about the mechanisms by which oral mifepristone or intravaginal misoprostol could potentiate C. sordellii infection or toxic shock syndrome. However, additional data are needed to evaluate further the possible association between medical abortion and C. sordellii infections, to define the spectrum of illness, and to identify risk factors for toxic shock syndrome.

The side effects of misoprostol (e.g., vomiting, diarrhea, and abdominal cramping) may be similar to the initial symptoms of toxic shock syndrome associated with C. sordellii. To improve diagnosis and therapy, clinicians should be aware of the distinctive features of this potentially fatal entity, including tachycardia, hypotension, edema, hemocoagulation, profound leukocytosis, and absence of fever. Health care providers should report to their state or local health department any cases of toxic shock syndrome occurring after an abortion or associated with pregnancy.

The views expressed are those of the authors and do not necessarily represent the views of the Department of Health and Human Services.

We are indebted to L. Lepine, R. Zamary, J. Tam, F. Lessa, D. Stephens, C. Paddock, J. Sumner, J. O’Connor, D. Jermigan, L.C. McDonald, and N. Rosenstein for their assistance with the investigation and review of the manuscript.

**REFERENCES**

28. Clostridium sordellii toxic shock syndrome occurring after an abortion or associated with pregnancy. The views expressed are those of the authors and do not necessarily represent the views of the Department of Health and Human Services.
29. We are indebted to L. Lepine, R. Zamary, J. Tam, F. Lessa, D. Stephens, C. Paddock, J. Sumner, J. O’Connor, D. Jermigan, L.C. McDonald, and N. Rosenstein for their assistance with the investigation and review of the manuscript.
brief report

fda.gov/cedr/drug/infopage/mifepristone/default.html.)
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Patent Foramen Ovale in Young Adults with Unexplained Stroke

Jorge R. Kizer, M.D., and Richard B. Devereux, M.D.

A 38-year-old man notes abrupt loss of vision in his right visual field while reading. He has no significant medical history and reports that he neither smokes nor uses alcohol or illicit drugs. Physical examination reveals right homonymous hemianopia but no other abnormalities. Magnetic resonance imaging reveals acute left occipital infarction and normal head and neck vessels. Transesophageal echocardiography shows a patent foramen ovale without atrial septal aneurysm. What are the implications of this finding, and what therapy should be recommended?

Stroke is a leading cause of death and long-term disability worldwide. Eighty-five percent of strokes are ischemic, and most ischemic strokes occur in persons older than 65 years of age in tandem with the development of atherosclerosis. Although a minority of ischemic strokes in the community affect younger adults, as many as half the patients referred to tertiary care centers are younger than 65 years of age, and up to 12 percent are younger than 45 years.

Young patients with ischemic stroke often have few, if any, risk factors for atherosclerosis.

Initial evaluation of the cerebral arteries is essential but frequently unrevealing, and thus in many cases the focus must shift to the detection of potential cardiac sources of embolism that are commonly associated with, and that may cause, unexplained stroke in young persons.

In as many as 43 percent of affected young adults, strokes are cryptogenic (i.e., they do not have a definite cause despite extensive evaluation). The most prevalent potential source of cardioembolism in young adults with cryptogenic stroke is patent foramen ovale, which is detected in more than half of such persons undergoing evaluation. This discussion focuses principally on patent foramen ovale occurring in young patients (those younger than 45 years old) or middle-aged patients (those 45 to 64 years old) who have minimal risk factors for atherosclerosis and in whom evaluations for vascular disease or systemic illnesses are negative. Other potential sources of cardioembolism in these patients are described in Table 1.

Patent foramen ovale, which is present in 27 percent of unselected adults, is a vestige of the fetal circulation and results from failure of the primum and secundum septa to fuse postnatally. Persistence of the one-way flap valve overlying the fossa ovalis allows right-to-left blood flow when right atrial pressure exceeds left atrial pressure (Fig. 1).

In support of the proposition that patent foramen ovale can serve as a gateway to the arterial circulation for venous thromboemboli, various studies have documented thrombus straddling the foramen in patients with deep-vein thrombosis and systemic em-
Table 1. Overview of Potential Cardiac Sources of Embolism Other Than Patent Foramen Ovale.

<table>
<thead>
<tr>
<th>Potential Source</th>
<th>Description</th>
<th>Associated Conditions and Risk Factors</th>
<th>Prevalence</th>
<th>Estimated Risk of Stroke</th>
<th>Possible Interventions and Evidence for Reduction in Risk of Stroke</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Cryptogenic Stroke</td>
<td></td>
<td>Patients with Cryptogenic Stroke</td>
<td>&lt;2%</td>
<td>High, but not quantifiable; one third of persons with myxoma present with systemic embolism; increased risk of papillary myxomas†</td>
<td>Surgical resection; anticoagulant or antiplatelet therapy of questionable benefit (no controlled data, but resection is required to eliminate risk of tumor-related embolism; tumor recurrence can occur, however, particularly in the Carney complex)</td>
<td>(6,7)</td>
</tr>
<tr>
<td>Myxoma</td>
<td>Neoplasm arising from endocardium, typically in left atrium (70%), where it is attached to fossa ovalis; usually polypoid and attached by pedicle, but may be papillary with gelatinous, fragile extensions</td>
<td>May be sporadic or familial, as part of the Carney complex</td>
<td>Approximately 0.01% (most common primary cardiac tumor, with 2:1 female predominance)</td>
<td>Not quantifiable, but appears to be directly proportional to size and mobility†</td>
<td>Surgical resection vs. antiplatelet or anticoagulant therapy (no controlled data, but consensus is that larger [≥1 cm], mobile lesions warrant surgical resection)</td>
<td>(7)</td>
</tr>
<tr>
<td>Papillary fibroelastoma (giant Lambl's excrescence)</td>
<td>Process of unclear cause (neoplastic, hamartomatous, or reparative); arises from valvular surfaces, typically left-sided valves (more often aortic than mitral); frondlike vs. circumscribed appearance; often a stalklike attachment</td>
<td>Unknown</td>
<td>Very low;‡ About 0.003% (second most common primary cardiac tumor, with a male:female ratio of about 1:1)</td>
<td>HR for recurrent stroke or death, 0.59; 95% CI, 0.08–4.43 (in older population with cryptogenic stroke)‡</td>
<td>Antiplatelet therapy (no evidence that anticoagulation is superior to antiplatelet therapy in reducing recurrent stroke or death)</td>
<td>(6,7,8)</td>
</tr>
<tr>
<td>Valvular strands (Lambl's excrescences)</td>
<td>Small filiform projections (width ≤1 mm, length ≤10 mm); arise near closure line of valves (mitral more often than aortic); result from traumatic abrasions of valve surface with fibrin deposition and endothelialization</td>
<td>Possibly age; intrinsic valvular disease; first described as a feature of rheumatic valve disease</td>
<td>38.8%</td>
<td>46.9%</td>
<td></td>
<td>(9,10)</td>
</tr>
</tbody>
</table>

References:
| Mitral-valve prolapse | Myxomatous degeneration of valve leaflets with billowing >2 mm past the annular plane in systole; malcoaptation results in mitral regurgitation | Connective-tissue disorders (Marfan’s and Ehlers–Danlos syndromes); genetic; volume depletion; mitral regurgitation leading to left atrial and ventricular enlargement, atrial fibrillation, and need for mitral-valve surgery; relation to interatrial septal abnormalities | 2.8% (<45 yr with stroke or TIA) | 2.4% (2.7% in women and 2.1% in men; mean age, 56 yr) | Younger age: OR for stroke or TIA, 1.06 (95% CI, 0.11–5.73) in patients <45 yr; 0.4% risk of TIA (0 strokes) at 10 yr and RR, 1.7 (95% CI, 0.4–9.5) in patients <50 yr vs. community-based rates. Older age: 16% risk of stroke or TIA and RR, 2.3 (95% CI, 1.5–3.3) in patients ≥50 yr vs. community-based rates. Risk related to leaflet thickness and severity of mitral regurgitation, with incident atrial fibrillation and mitral-valve surgery responsible in large measure for incident cerebral ischemia. | Antiplatelet therapy, with anticoagulant therapy as an alternative (no controlled data to support added benefit of anticoagulation therapy); valve repair or replacement in setting of severe regurgitation, as indicated |

| Intrapulmonary shunt | PAVM | HHT; liver disease | Very low | Not quantified (70% in patients with HHT; conversely, 25% of patients with HHT have PAVM) | Not quantifiable, but appears substantial for PAVM ≥3 mm† | Percutaneous coil embolization for PAVM ≥3 mm in diameter; anticoagulation is alternative option for large PAVM (no controlled data) |

| Aortic-arch thrombosis | Thrombus attached to simple atheroma in the aortic arch, which otherwise exhibits no or minimal evidence of atherosclerotic disease | Risk factors for atherosclerosis; possibly hypercoagulable states | Very low | Not quantified | High, but not quantifiable | Anticoagulant therapy; surgical embolectomy with patch repair and percutaneous balloon emboloclysis are alternatives (no controlled data) |

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* The information shown is limited to cardioembolic sources in patients with normal sinus rhythm and no or minimal atherosclerosis; without ischemic, valvular, or congenital heart disease; and without systemic inflammatory states, cancer, or infection. HR denotes hazard ratio, CI confidence interval, TIA transient ischemic attack, OR odds ratio, RR relative risk, HHT hereditary hemorrhagic telangiectasia, and PAVM pulmonary arteriovenous malformation.

† The available data are based on case series and case reports.

‡ Prevalence is well below 1 percent, but precise estimation was not possible.

§ The available data are based on case–control studies. These data showed an association, which was not reproduced in longitudinal studies or in a substudy of randomized trial of aspirin as compared with warfarin for noncardioembolic stroke, although the latter studies had limited power.

¶ Early reports of an association in persons younger than 45 years of age used an older, less specific, definition of mitral-valve prolapse; the data have not been confirmed according to an updated definition, but studies are underpowered.

‖ The available data are based on a single case series.
bolism.\textsuperscript{17} Such “thrombus-in-transit,” however, is rarely detected in patients with stroke and patent foramen ovale, and the clinical diagnosis of paradoxical embolism instead depends on the concurrence of arterial embolism, venous thrombosis, interatrial communication, and a gradient favoring right-to-left shunting.\textsuperscript{18}

An important role for patent foramen ovale in the pathogenesis of ischemic stroke was first suggested by a case–control study that showed a markedly higher frequency of patent foramen ovale (detected by transthoracic echocardiography) in patients with cryptogenic stroke who were younger than 55 years of age than in controls (54 percent vs. 10 percent).\textsuperscript{5} A meta-analysis of case–control studies subsequently confirmed an increased prevalence of patent foramen ovale among patients 55 years of age or younger with cryptogenic stroke as compared with stroke-free controls (odds ratio, 5.01; 95 percent confidence interval, 3.24 to 7.75)\textsuperscript{19} but not among persons 55 years of age or older (odds ratio, 1.20; 95 percent confidence interval, 0.56 to 2.56).\textsuperscript{19}

Many of these studies, however, lacked blinded interpretation of echocardiograms — a limitation that may have led to ascertainment bias. Furthermore, the studies compared patients and controls who had been referred for echocardiography for different indications and hence were susceptible to biases related to varying thoroughness in the assessment of patent foramen ovale or associated anatomical features. Nevertheless, a significant association between patent foramen ovale and cryptogenic stroke has since been documented in a prospective clinical trial in which ascertainment of patent foramen ovale was made without knowledge of the participants’ clinical history.\textsuperscript{20}

Despite this association, the etiologic role of patent foramen ovale in cryptogenic stroke has been questioned.\textsuperscript{21} Paradoxical embolism, the presumptive mechanism, requires a favorable pressure gradient for right-to-left shunting, but such a gradient normally occurs only transiently, in early systole.\textsuperscript{22} Moreover, conditions that promote right-to-left shunting, such as pulmonary hypertension or Valsalva-inducing activities, are rarely documented in patients with stroke who have patent foramen ovale.\textsuperscript{21}

In addition, evaluation of patients with cryptogenic stroke and patent foramen ovale rarely reveals a venous source of thrombus.\textsuperscript{21} The reportedly low rate of detection of deep-vein thrombosis, however, may reflect delays in imaging, which often was performed after the initiation of anticoagulation.\textsuperscript{23} Furthermore, the absence of a detectable venous thrombus is not unique to patients with
stroke and patent foramen ovale. In 20 to 30 percent of patients with pulmonary embolism, deep-vein thrombi are not identified. Failure to detect a thrombus in such patients may be attributable to complete thrombus migration, inability to detect residual thrombus, or undetected thrombosis in a calf or pelvic vein. In a venographic study involving 42 patients with arterial embolism and patent foramen ovale, deep-vein thrombosis was documented in 24 of the patients; in 13, thrombosis was identified only in calf veins. This finding raises the possibility that calf-vein thrombi, which must generally extend proximally before causing clinically important pulmonary embolism, may be able to discharge small embolic fragments (1 mm in diameter) that are sufficient to cause a clinical stroke should they gain access to the arterial circulation. In another study, pelvic-vein thrombi were documented by magnetic resonance venography in 20 percent of patients with cryptogenic stroke who had patent foramen ovale.

Nevertheless, the difficulty of confirming the occurrence of paradoxical embolism has led to the consideration of alternative explanations, such as in situ thrombosis or atrial tachyarrhythmia. The former, however, is very rarely found by transesophageal echocardiography or at autopsy. Moreover, although patients with interatrial septal abnormalities and stroke have lower thresholds for the induction of atrial fibrillation, this arrhythmia is almost never documented in patients with cryptogenic stroke and patent foramen ovale.

Adding to the mechanistic uncertainty, population-wide figures suggest that the yearly risk of cryptogenic stroke in healthy persons with patent foramen ovale may be as low as 0.1 percent. This observation suggests that additional factors may be necessary to increase the associated risk of stroke. Features of the patent foramen ovale may be important. A large anatomical separation (4 mm or more) between the primum and secundum septa, increased right-to-left shunting or shunting at rest, increased septal mobility, and the presence of an atrial septal aneurysm have been linked to an increased risk of stroke, but ascertainment bias remains possible. Moreover, the clinical relevance of patent foramen ovale is influenced by concurrent risk factors for venous thromboembolism, such as trauma, recent surgery, use of oral contraceptives, and hypercoagulable states.

Atrial Septal Aneurysm

The prevalence at autopsy of atrial septal aneurysm, caused by redundancy of the interatrial septum (Fig. 2), is 1 percent. A relation between atrial septal aneurysm and stroke has been documented, with one study reporting a greater prevalence among persons with stroke (7.9 percent) than among population-based controls (2.2 percent) on transesophageal echocardiography. Detection of thrombi in situ on the interatrial septum led to the notion that the redundant membrane promotes thrombogenesis, but in situ thrombosis is seen only rarely. Alternative explanations for the increased risk of stroke in patients with atrial septal aneurysms are the high prevalence (50 to 90 percent) of coexisting patent foramen ovale, especially larger foramina, or of an atrial septal defect (as shown in Video Clip 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Moreover, atrial septal aneurysms are associated with prominent eustachian valves or Chiari networks, right atrial membranes that facilitate right-to-left shunting by directing flow from the inferior vena cava toward the fossa ovalis, and with tachyarrhythmias predisposing to thromboembolism.

Strategies and Evidence

Evaluation

Transesophageal echocardiography is superior to transthoracic echocardiography for the detection of potential sources of cardioembolism. Although transthoracic echocardiography identifies such sources in about 25 percent of patients with clinically apparent cardiac disease, its yield in patients without cardiac signs or symptoms is less than 10 percent. By contrast, transesophageal echocardiography detects potential sources of cardioembolism in as many as 57 percent of patients with unexplained stroke. Intravenous injection of saline mixed with air greatly enhances the diagnosis of right-to-left shunts by transthoracic or transesophageal echocardiography by permitting visualization of microbubbles in the chambers of the left side of the heart that would otherwise be filtered by the lung capillaries. The sensitivities of traditional transthoracic echocardiography with agitated-saline contrast agent for right-to-left shunts and atrial septal aneurysm are at...
most half those of contrast-based transesophageal echocardiography, but recent refinements (for example, a contrast-based transmitral Doppler technique) have improved its diagnostic accuracy. Another alternative, contrast transcranial Doppler sonography, in which imaging of the middle cerebral arteries is used to detect right-to-left shunting of microbubbles, offers accuracy similar to that of transesophageal echocardiography. Its utility, however, is limited by its inability to assess interatrial septal morphologic features or other cardiac structures. Although transesophageal echocardiography is semi-invasive, it is associated with a low risk of serious complications (0.2 percent), which may include bronchospasm, hypoxia, arrhythmias, upper gastrointestinal trauma, or bleeding.

Formal analyses of the optimal use of echocardiography in young patients with cryptogenic stroke are lacking. Nevertheless, the increased diagnostic yield of transesophageal echocardiography as compared with that of transthoracic echocardiography or transcranial Doppler sonography supports the use of the transesophageal technique in this population, pending further evidence regarding the benefits of treating specific lesions found on echocardiography.

TREATMENT

The available evidence on pharmacologic approaches (involving the use of antiplatelet or anticoagulant agents) and mechanical approaches to secondary prevention in patients with cryptogenic stroke who have patent foramen ovale is inadequate for assessment of their relative merits. To date, no study has randomly assigned patients with cryptogenic stroke and patent foramen ovale to different therapies. Studies thus far have been observational, with disparate definitions of the qualifying or recurrent cerebrovascular event, nonuniform criteria for interatrial septal abnormalities, absence of blinding during examination of echocardiograms or ascertainment of end points, and incomplete accounting of associated risk factors or the use of adjunctive therapies.

The risk of stroke recurrence in patients 60 years of age or younger who have unexplained cerebral ischemia and patent foramen ovale appears to be low, regardless of the therapy used. In a prospective study of 140 such patients treated medically or surgically at their physicians’ discretion, the annual rate of stroke recurrence was 1.9 percent, and the type of treatment had no detectable influence. Similarly, a longitudinal study of 581 persons 55 years of age or younger who had cryptogenic stroke treated with aspirin found similarly low rates of recurrence at four years among those who had a patent foramen ovale (2.3 percent) and those who did not (4.2 percent). Patients who had both patent foramen ovale and atrial septal aneurysm, however, had a 15.2 percent rate of recurrence despite the use of aspirin therapy — a rate nearly fourfold that...
among patients who did not have either abnormality. Unlike prior investigations, this study found that a greater shunt magnitude was not associated with increased risk, but the study had limited power to assess the relative effects of foraminal size and atrial septal aneurysm.\textsuperscript{33}

By contrast, in a randomized trial in which aspirin therapy and warfarin therapy were compared in older patients with stroke, the two-year rate of recurrent stroke or death in the subgroup with cryptogenic stroke was not significantly higher among those who had a patent foramen ovale and atrial septal aneurysm than among those with neither abnormality.\textsuperscript{38} However, the study was underpowered for this comparison, and patients without interatrial septal abnormalities had more risk factors for subclinical atherosclerotic disease than did those with those abnormalities. Post hoc analyses\textsuperscript{43} of data from this study indicated that there was no significant association between patent foramen ovale and the risk of recurrent stroke or death among patients younger than 65 years of age but an association was observed in older patients. These findings, however, are limited by the small numbers of events in each subgroup and by the performance of multiple comparisons that were not prespecified.

**Medical Therapy**

In a retrospective study of 90 patients younger than 60 years of age with cerebral ischemia, 52 of whom had patent foramen ovale, those receiving aspirin or no therapy had a rate of recurrence almost threefold that of patients treated with warfarin.\textsuperscript{44} (The numbers were too small to allow comparison between the group that received aspirin and the group that did not receive therapy.) The results are inconclusive, however, for several reasons: treatment assignments were at the discretion of the consulting neurologist; treatment crossover was frequent; and ascertainment of end points, which included multiple events, was not blinded. For similar reasons, it is impossible to draw firm conclusions from a meta-analysis that found that warfarin (as compared with antiplatelet therapy) lowered the risk of recurrence (odds ratio, 0.37; 95 percent confidence interval, 0.23 to 0.60) among patients with cerebral ischemia and patent foramen ovale.\textsuperscript{45} In a randomized trial, subgroup analysis of 98 patients with cryptogenic stroke and patent foramen ovale revealed a nonsignificant reduction in the two-year incidence of recurrent stroke or death with warfarin therapy as compared with aspirin therapy (9.5 percent vs. 17.9 percent; hazard ratio, 0.52; 95 percent confidence interval, 0.16 to 1.67), but the power of the analysis was limited.\textsuperscript{20} Although the incidence of major hemorrhage did not differ between warfarin and aspirin (1.78 vs. 1.91 events per 100 patient-years, P=1.0), warfarin did increase the rate of minor hemorrhage (22.9 vs. 8.66 events per 100 patient-years, P<0.001).\textsuperscript{20}

**Mechanical Closure**

The traditional approach to foraminal closure involves open thoracotomy. Reported case series are small, but the rate of postoperative stroke ranges from 0 to 3.5 percent\textsuperscript{46-48} at two years. The mortality associated with closure of an uncomplicated atrial septal defect is less than 1.5 percent.\textsuperscript{49} Perioperative risks also include atrial fibrillation, pericardial sequelae, and the need for reexploration because of bleeding.\textsuperscript{46-48} Minimally invasive surgery\textsuperscript{50} is an alternative approach, but percutaneous-closure techniques hold greater appeal (Fig. 3). A systematic review found that among 1355 patients undergoing percutaneous closure, the rate of recurrent stroke or transient ischemic attack was 0 to 4.9 percent at one year.\textsuperscript{51} Although these values appeared favorable next to one-year recurrence rates among 895 patients receiving medical therapy (3.8 to 12.0 percent),\textsuperscript{51} several considerations — the nonrandomized treatment assignment, differences in the clinical characteristics of the patients treated by the various techniques, and inconsistent criteria for ascertainment of outcomes — preclude meaningful comparison. Serious complications of percutaneous closure (major hemorrhage, cardiac tamponade, the need for surgery, pulmonary embolism, and death) were reported in 1.5 percent of the patients, and minor complications (arrhythmia, device fracture or embolization, air embolism, femoral hematoma, and fistula) in 7.9 percent.\textsuperscript{51}

In one follow-up study of young patients with cryptogenic stroke and patent foramen ovale, surgical closure was performed if at least two of four purported “high-risk” features for paradoxical embolism (major shunt [>50 bubbles], atrial septal aneurysm, infarcts in multiple territories, and Valsalva-provoking activity preceding the onset of stroke\textsuperscript{22}) were present. There were no recurrences after 23 months, but the study did not include a control group.\textsuperscript{46} A decision analysis modeling different therapeutic approaches in a 55-year-old
A patient with patent foramen ovale concluded that, for a yearly risk of stroke recurrence of 0.8 percent, surgical closure or warfarin were the best options.\(^4^9\) (Percutaneous closure was not considered.) Surgery became preferable when the annual risk of recurrence reached 1.4 percent. These conclusions, however, rest on the questionable assumptions that paradoxical embolism underlies the risk of stroke and that anticoagulation lowers the risk of recurrence to the same degree as it does in persons with

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**Figure 3. Percutaneous Closure of a Patent Foramen Ovale.**

With use of a femoral approach, a transvenous sheath is advanced across the foramen into the left atrium, where a folded disk is expanded and pulled back, apposing the primum and secundum septa closed. This step is followed by deployment of a right-sided disk, at which time the two-disk device is released. Clopidogrel and aspirin are recommended for a period of three months to prevent thrombus formation on the device, with aspirin therapy continued for an additional three months, when endothelialization is complete. Antibiotic prophylaxis for six months is recommended. Complete late closure of the foramen has been reported in 80 to 95 percent of patients.
Table 2. Guidelines from Professional Societies.

<table>
<thead>
<tr>
<th>Purpose and Technique</th>
<th>American College of Cardiology/American Heart Association/American Society of Echocardiography53</th>
<th>American Academy of Neurology54</th>
<th>American College of Chest Physicians55</th>
</tr>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>Class I: younger patients (typically &lt;45 yr) with cerebrovascular events; older patients (typically &gt;45 yr) with neurologic events without evidence of cerebrovascular disease or other obvious cause; patients for whom a clinical therapeutic decision (e.g., anticoagulation) will depend on results of echocardiography†</td>
<td>Combination of patent foramen ovale and atrial septal aneurysm may confer increased risk of subsequent stroke in medically treated patients &lt;55 yr; thus, in younger patients with stroke, studies that can identify patent foramen ovale or atrial septal aneurysm may be considered for prognostic purposes (level C)‡</td>
<td>—</td>
</tr>
<tr>
<td>TTE vs. TEE</td>
<td>No specific recommendations. When positive, TTE considered sufficient for diagnosis of mitral stenosis, dilated cardiomyopathy, left ventricular aneurysm, left ventricular thrombus, mitral-valve prolapse, vegetation, or atrial septal defect. But TEE may be additive when TTE is negative. TEE required primarily or alone for diagnosis of left atrial thrombus, left atrial spontaneous contrast, atrial septal aneurysm, patent foramen ovale, or aortic atheroma</td>
<td>—</td>
<td>No specific recommendations. TEE more sensitive than TTE for detecting cardioembolic sources, particularly when searching for left atrial sources, atrial septal defects, and aortic atheroma</td>
</tr>
<tr>
<td>Management</td>
<td>Evidence insufficient to determine whether warfarin or aspirin is superior in preventing recurrent stroke or death (level U),§ but minor bleeding is more frequent with warfarin (level C)‡; there is insufficient evidence to evaluate the efficacy of surgical or endovascular closure (level U)§</td>
<td>Antiplatelet therapy recommended over no therapy (grade 1C+) and antiplatelet therapy suggested over warfarin (grade 2A)¶</td>
<td>Inadequate data available to allow recommendation of optimal medical therapy (anticoagulation or antiplatelet therapy) vs. endovascular or surgical closure</td>
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<tr>
<td>Patent foramen ovale</td>
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<tr>
<td>Patent foramen ovale alone</td>
<td>—</td>
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<tr>
<td>Patent foramen ovale in combination with other risk factors (e.g., hypercoagulability or atrial septal aneurysm)</td>
<td>—</td>
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</tr>
<tr>
<td>Patent foramen ovale with concomitant deep-vein thrombosis or pulmonary embolism</td>
<td>—</td>
<td>At least 3 mo of anticoagulation</td>
<td>Anticoagulation recommended</td>
</tr>
</tbody>
</table>

* Dashes indicate that no recommendations are provided. TTE denotes transthoracic echocardiography, and TEE transesophageal echocardiography.
† Class I indicates that there is evidence, general agreement, or both that a given procedure or treatment is useful or effective.
‡ Level C indicates that the recommendation or statement is qualified as possible.
§ Level U indicates that the data are inadequate or conflicting. Given current knowledge, the treatment is unproven.
¶ Grade 1C+ indicates a strong recommendation; experts are very certain that the benefits of therapy do outweigh the risks, burdens, and costs on the basis of overwhelming evidence from observational studies. Grade 2A is a weaker recommendation, qualified as a suggestion, and is based on consistent results from randomized clinical trials.
venous thromboembolism or atrial fibrillation. Currently, the Food and Drug Administration allows the use of transcatheter-closure devices under a humanitarian device exemption only in cases of recurrence of stroke during therapeutic oral anticoagulation.\textsuperscript{52}

### Areas of Uncertainty

The pathogenesis of cryptogenic stroke in patients with interatrial septal abnormalities is not well understood. Features of the interatrial septum that best predict the risk of thromboembolism and the role of hypercoagulable disorders in determining risk also remain unclear. Data from ongoing randomized trials that evaluate warfarin, aspirin, or both as compared with transcatheter closure are needed. Pending completion of such studies, which have been hampered by slow recruitment,\textsuperscript{52} the relative safety and efficacy of these approaches remain uncertain.

### Guidelines

Current guidelines from professional societies (Table 2) do not include specific recommendations regarding the optimal diagnostic strategy for transesophageal and transesophageal echocardiography.\textsuperscript{53} Moreover, they deem the available evidence insufficient to permit firm recommendations for the management of interatrial septal abnormalities.\textsuperscript{54,55}

### Conclusions and Recommendations

In patients with cryptogenic stroke, assessment for patent foramen ovale and other potential cardiac sources of embolism is recommended; transesophageal echocardiography is more sensitive for detecting these abnormalities than is transthoracic echocardiography. Because the presumed pathophysiology of cryptogenic stroke in younger patients with patent foramen ovale is paradoxical embolism of fibrin-rich thrombus, and because observational data suggest a benefit with warfarin relative to aspirin, we would consider the use of warfarin anticoagulation for three to six months in patients such as the man described in the vignette. Available data are not sufficient for confirmation that this approach is preferable to aspirin therapy, however, and current guidelines do not specifically recommend one over the other.\textsuperscript{54,55} Appropriate investigation for deep-vein thrombosis and thrombophilia is essential. We recommend switching most patients’ therapy to aspirin after they have received a course of warfarin. However, we favor long-term anticoagulation in patients with associated venous thromboembolism or selected hypercoagulable states and probably in patients with high-risk features (atrial septal aneurysm, major shunt, infarcts in multiple territories, or antecedent Valsalva-provoking activity).

Decisions must take into account coexisting conditions and the patients’ preferences. Patients should be encouraged to participate in ongoing randomized trials comparing percutaneous closure and medical therapy. Otherwise, percutaneous closure is currently indicated in the United States only for patients with recurrence despite therapeutic anticoagulation. Surgical closure may be considered for high-risk patients when warfarin is contraindicated.

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CLINICAL PRACTICE


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**Low-Dose Aspirin for the Prevention of Atherothrombosis**

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**THROSCLESOSIS, THE MAJOR CAUSE OF ISCHEMIC CORONARY ARTERY disease and cerebrovascular disease, is a chronic inflammatory disorder in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate vascular lesions.**

Arterial thrombosis, an acute complication that develops on the surface of a ruptured atheromatous plaque or as a consequence of endothelial erosion, may cause myocardial infarction or ischemic stroke. Platelets are key cellular components of arterial occlusive thrombi and may participate in the development and progression of atheromatous plaques. Platelets are also vital components of hemostasis, the physiologic process that arrests hemorrhage after tissue trauma and vascular injury. Although the adhesion and activation of platelets can be viewed as a repair-oriented response to sudden fissuring or rupture of an atheromatous plaque, uncontrolled progression of such a process through a series of self-sustaining amplification loops may lead to the intraluminal formation of thrombus, vascular occlusion, and transient ischemia or infarction. The ability of platelets to participate in both normal hemostasis and atherothrombosis depends on their adhesive properties and their capacity to become activated very quickly in response to various stimuli.

Currently available antiplatelet drugs interfere with certain steps in the activation process by selectively blocking key platelet enzymes or receptors, reducing the risk of arterial thrombosis through mechanisms that cannot be dissociated from an increased risk of bleeding complications. In particular, randomized trials indicate that low-dose aspirin can prevent arterial thrombosis under various circumstances, including first vascular events among low-risk, healthy subjects and recurrent vascular events among patients with known acute or chronic occlusive vascular disease.

The aim of this review is to integrate our current understanding of the molecular mechanism of action of aspirin with the results of clinical trials and epidemiologic studies of aspirin as an antiplatelet agent, placing special emphasis on the benefits and risks in various patient populations.

**PHARMACOKINETICS**

Aspirin is rapidly absorbed in the stomach and upper small intestine, primarily by passive diffusion of nondissociated acetylsalicylic acid across gastrointestinal membranes. Plasma levels peak 30 to 40 minutes after the ingestion of uncoated aspirin. In contrast, it can take up to three or four hours for plasma levels to peak after the administration of enteric-coated formulations; thus, patients should chew these preparations if a rapid antiplatelet effect is required. Esterases hydrolyze aspirin in the gastrointestinal mucosa and the liver, forming salicylic acid. The oral bioavailability of regular aspirin tablets is approximately 40 to 50 percent over a wide range of doses, but the bioavailability of enteric-coated tablets and sustained-release, microencapsulated preparations is...
considerably lower. Aspirin first comes into contact with platelets in the portal circulation, and as a consequence, platelets are exposed to substantially higher drug levels than are present in the systemic circulation. Aspirin has a half-life of 15 to 20 minutes in plasma.

Despite the rapid clearance of aspirin from the circulation, its antiplatelet effect lasts for the life of a platelet owing to the permanent inactivation of a key platelet enzyme, an effect that can be reversed only through the generation of new platelets. Thus, there is a complete dissociation between the pharmacokinetics and pharmacodynamics of aspirin, allowing the use of a once-a-day regimen for antiplatelet therapy despite the very short half-life of the drug.

**MECHANISM OF ACTION**

The best-characterized mechanism of action of aspirin occurs through permanent inactivation of the cyclooxygenase (COX) activity of prostaglandin H (PGH) synthase 1 and synthase 2, also referred to as COX-1 and COX-2, respectively (Fig. 1). These

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**Figure 1. Mechanism of Action of Aspirin.**

Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the sn2 position of membrane phospholipids by several forms of phospholipase A2, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin H synthases, which have both cyclooxygenase and hydroperoxidase (HOX) activity, to the unstable intermediates prostaglandin G2 and prostaglandin H2, respectively. The synthases are colloquially termed cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Low-dose aspirin selectively inhibits COX-1, whereas high-dose aspirin inhibits both COX-1 and COX-2. Prostaglandin H2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein–coupled receptors, such as the thromboxane receptor, the prostaglandin D2 receptors, the prostaglandin E2 receptors, the prostaglandin F2α receptors, and the prostacyclin receptor.
isoenzymes catalyze the first committed step in prostanoid biosynthesis — the conversion of arachidonic acid to PGH₂. PGH₂ is an unstable biosynthetic intermediate and a substrate for several downstream isomerases that generate at least five different bioactive prostanoids, including thromboxane A₂ (TXA₂) and prostacyclin (PGI₂).

By diffusing through cell membranes, aspirin enters the COX channel, a narrow hydrophobic channel connecting the cell membrane to the catalytic pocket of the enzyme. Aspirin first binds to an arginine-120 residue, a common docking site for all nonsteroidal antiinflammatory drugs; it then acetylates a serine residue (serine 529 in human COX-1 and serine 516 in human COX-2) located in the narrowest section of the channel, thereby preventing arachidonic acid from gaining access to the COX catalytic site of the enzyme. Higher levels of aspirin are needed to inhibit COX-2 than to inhibit COX-1. These differences may account, at least in part, for the need to use considerably higher doses of aspirin to achieve analgesic and antiinflammatory effects, whereas antiplatelet effects can be obtained with daily doses as low as 30 mg.

**FUNCTIONAL CONSEQUENCES OF THE EXPRESSION AND INHIBITION OF CYCLOOXYGENASE**

Although newly formed platelets express both COX-1 and COX-2, mature platelets express only COX-1. In contrast, vascular endothelial cells express both COX-1 and COX-2. The latter is up-regulated in response to physiologic hemodynamics and is the predominant source of PGI₂ in health and disease. Platelets and vascular endothelial cells process PGH₂ to produce primarily TXA₂ and PGI₂, respectively. TXA₂ is synthesized and released by platelets in response to a variety of stimuli (for example, collagen, thrombin, and adenosine diphosphate) and, in turn, induces irreversible platelet aggregation through its interaction with a G-protein–coupled receptor, the TXA₂ receptor. Thus, TXA₂ provides a mechanism for amplifying the responses of platelets to diverse agonists. In addition, TXA₂ is a potent vasoconstrictor that induces the proliferation of vascular smooth-muscle cells, and is proatherogenic. In contrast, PGI₂ inhibits platelet aggregation in response to all agonists through its interaction with the PGI₂ receptor. PGI₂ also induces vasodilation, inhibits the proliferation of vascular smooth-muscle cells, protects the myocardium against oxidant stress, and is anti-atherogenic. Deletion of the gene encoding the PGI₂ receptor is associated with increased susceptibility to experimental thrombosis, thus supporting the importance of PGI₂ in vascular thromboresistance.

Although TXA₂ is a prostanoid largely derived from COX-1 (mostly from platelets) and its biosynthesis is highly sensitive to inhibition by aspirin, vascular PGI₂ is derived predominantly from COX-2 and is less susceptible to inhibition by low doses of aspirin. Aspirin induces a long-lasting functional defect in platelets that can be detected clinically as a prolonged bleeding time. In contrast, low-dose aspirin has no measurable effects on PGI₂-dependent vascular functions; thus, it does not increase blood pressure, impair renal function, or interfere with the antihypertensive effects of diuretics and angiotensin-converting–enzyme (ACE) inhibitors.

Although other mechanisms have been proposed, inhibition of platelet COX-1 is sufficient to explain the antithrombotic effects of low-dose aspirin. This does not necessarily imply that a single mediator, TXA₂, is responsible for the one quarter of major vascular events that can be prevented by low-dose aspirin in high-risk patients, because inhibition of platelet activation at sites of vascular injury may have indirect consequences, such as reducing the release of inflammatory cytokines, oxygen radicals, growth factors, and other proteins. Moreover, reduced release of these diverse platelet products may contribute, at least in part, to interference with other disease processes in which the efficacy and safety of low-dose aspirin are currently being investigated. In fact, the efficacy of once-a-day regimens of low-dose aspirin in preventing the recurrence of colorectal adenoma is consistent with the hypothesis that activated platelets induce the up-regulation of COX-2 in one or more types of cells involved in early intestinal carcinogenesis.

**CLINICAL PHARMACOLOGY OF THE INHIBITION OF PLATELET CYCLOOXYGENASE**

The effects of aspirin on the activity of platelet COX-1 have been characterized through measurements of serum thromboxane B₂ (TXB₂) and urinary metabolites of TXB₂. Three important features of these effects should be emphasized: the cumulative nature of the inactivation of platelet COX-1 with repeated daily doses of aspirin, the saturaibility of this effect, and the selectivity for
COX-1 at low doses.\textsuperscript{18,31} Thus, the daily administration of 30 mg of aspirin results in virtually complete suppression of platelet TXA\textsubscript{2} production after one week\textsuperscript{38} through a cumulative process of fractional acetylation of roughly 50 percent of unacetylated platelet COX-1 by successive daily doses of aspirin.\textsuperscript{31} The practical implication of this finding is that typical regimens of 75 to 100 mg of aspirin per day clearly exceed the minimal effective dose required for a full pharmacodynamic effect, thus accommodating some degree of interindividual variability in drug response. There is no evidence that the pharmacodynamics of platelet inhibition by aspirin is any different in women than in men.\textsuperscript{18,31}

Because the maximal biosynthetic capacity of human platelets\textsuperscript{33} (Fig. 2A) is several thousand times as high as the basal rate of TXA\textsubscript{2} biosynthesis in healthy subjects\textsuperscript{34} (Fig. 2B), the relationship between the inhibition of platelet COX-1 activity and TXA\textsubscript{2} biosynthesis in vivo is strikingly nonlinear\textsuperscript{35} (Fig. 2C). The inhibition of platelet COX-1 attains functional relevance when the maximal capacity to generate TXA\textsubscript{2} is reduced by at least 95 percent.\textsuperscript{35,36}

The relative COX-1 selectivity of low-dose aspirin most likely accounts for the substantial residual COX-2–dependent PGI\textsubscript{2} biosynthesis in vivo at daily doses in the range of 20 to 80 mg.\textsuperscript{19} Despite transient suppression of COX-1–dependent release of PGI\textsubscript{2},\textsuperscript{37} More profound suppression of PGI\textsubscript{2} formation by higher doses of aspirin, as a function of the dose-dependent inhibition of COX-2, might be expected to attenuate the antithrombotic efficacy of the drug. However, there is limited direct evidence supporting this possibility.\textsuperscript{38-40}

Permanent inactivation of platelet COX-1 by aspirin may lead to bleeding complications as well as the prevention of arterial thrombosis. At least two distinct COX-1–dependent mechanisms contribute to the increased risk of upper gastrointestinal bleeding associated with aspirin therapy: the inhibition of TXA\textsubscript{2}-mediated platelet aggregation and the impairment of PGE\textsubscript{2}- and PGI\textsubscript{2}-mediated cytoprotection in the gastrointestinal mucosa.\textsuperscript{3} Whereas the former effect is independent of a dose in excess of 30 mg daily, the latter effect is clearly dose-dependent. Inhibition of platelet function may largely account for the twofold increase in the risk of upper gastrointestinal bleeding associated with daily doses of aspirin in the range of 75 to 100 mg, inasmuch as a similar relative risk is associated with other drugs that interfere with primary hemostasis but do not affect COX-dependent cytoprotection.\textsuperscript{41} Dose-dependent inhibition of cytoprotection by higher doses of aspirin amplifies the risk of bleeding and perforation by causing new mucosal lesions or aggravating existing ones and increases the risk by a factor of 4 to 10 at analgesic doses. The use of an antisecretory agent (especially a proton-pump

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**Figure 2.** Maximal Capacity of Human Platelets to Synthesize Thromboxane B\textsubscript{2} (TXB\textsubscript{2}) (Panel A), Rate of TXB\textsubscript{2} Production in Healthy Subjects (Panel B), and Nonlinear Relationship between the Inhibition of Platelet Cyclooxygenase Activity and TXB\textsubscript{2} Biosynthesis in Vivo (Panel C).

Panel A depicts the level of TXB\textsubscript{2} production stimulated by endogenous thrombin during whole-blood clotting at 37°C and is based on data from Patrono et al.\textsuperscript{33} Panel B shows the metabolic fate of thromboxane A\textsubscript{2} (TXA\textsubscript{2}) in vivo and the calculated rate of its production in healthy subjects on the basis of TXB\textsubscript{2} infusions and measurement of its major urinary metabolite.\textsuperscript{34} Panel C depicts the nonlinear relationship between the inhibition of serum TXB\textsubscript{2} measured ex vivo and the reduction in the excretion of thromboxane metabolites measured in vivo.\textsuperscript{35}
COX-1 inhibitors, such as ibuprofen, was associated with a reduced risk of upper gastrointestinal bleeding in patients taking aspirin in a case–control study, but no adequately sized placebo-controlled, randomized trial has examined the protective effects of acid-antisecretory therapy in patients treated with 75 to 100 mg of aspirin daily.

**Drug Interactions**

In contrast to treatment with the vast majority of COX inhibitors, low-dose aspirin therapy (75 mg daily) does not affect blood-pressure control or the need for antihypertensive therapy in patients with intensively treated hypertension. This observation is consistent with the absence of an effect of low-dose aspirin on renal prostaglandin synthesis. In humans, renal synthesis of prostaglandins is dependent on constitutively expressed COX-2. The suggestion that the benefit of ACE inhibitors after acute myocardial infarction may be reduced by aspirin is not supported by the results of a large meta-analysis of myocardial infarction trials. Similarly, no negative interaction occurs between ACE inhibition and the cardioprotection afforded by low-dose aspirin in patients with hypertension, and a meta-analysis of six long-term randomized trials comparing an ACE inhibitor with placebo did not show that aspirin use abrogated the benefits of ACE inhibitors. Thus, it appears that ACE inhibitors are beneficial irrespective of aspirin use.

A pharmacodynamic interaction that potentially interferes with the antiplatelet effect of aspirin is related to the two-step mechanism of COX-1 inactivation. Concomitant administration of reversible COX-1 inhibitors, such as ibuprofen and naproxen, may prevent the irreversible acetylation of platelet COX-1 by low-dose aspirin. This is due to competition between these drugs and aspirin for a common docking site within the COX-1 channel (arginine 120); aspirin binds this site with weak affinity before the acetylation of serine 529. This pharmacodynamic interaction does not occur with coxibs or traditional nonsteroidal antiinflammatory drugs (NSAIDs) such as diclofenac that have some degree of COX-2 selectivity. Whether this interaction attenuates or abrogates the cardioprotective benefit of low-dose aspirin is uncertain.

Low-dose aspirin therapy can cause upper gastrointestinal bleeding. In two large trials, subgroup analyses suggested that aspirin may attenuate the gastrointestinal safety of selective COX-2 inhibitors, as compared with traditional NSAIDs. However, this potential interaction needs to be assessed further in studies that compare selective COX-2 inhibitors with traditional NSAIDs in patients who are receiving aspirin.

**Aspirin Resistance**

The term “aspirin resistance” has been used to describe the inability of aspirin to produce a measurable response on ex vivo tests of platelet function, to inhibit TXA2 biosynthesis in vivo, or to protect individual patients from thrombotic complications. Similar phenomena have been described for clopidogrel, which is a thienopyridine with a totally different mechanism of action from that of aspirin. The term “resistance” does not describe the mechanisms underlying interindividual variability in response to aspirin or clopidogrel. In fact, it is potentially misleading, implying that something can be measured that has a direct bearing on clinical efficacy and that, depending on the results, may lead to a change in antiplatelet therapy. However, the relevance to in vivo platelet activation of the various ex vivo functional indexes of platelet capacity is largely unknown. Moreover, the correlations between results of different tests of aspirin responsiveness are poor. Thus, we think that the term “resistance” should be abandoned. Rather, the distinct factors that contribute to interindividual variability in response to aspirin or clopidogrel should be explored. For aspirin, these include the pharmacodynamic interaction with reversible COX-1 inhibitors, as noted above, as well as the role of extraplatelet sources of TXA2 production in different clinical settings.

As with any drug used to prevent atherothrombosis, vascular events are frequent among patients treated with aspirin or other antiplatelet drugs, and this phenomenon is sometimes described as treatment failure. Given the multifactorial nature of atherothrombosis, it is not surprising that less than a quarter of all vascular complications typically can be prevented through the use of any one strategy. There is no scientific basis for changing antiplatelet therapy in the face of such treatment failure, since we cannot be sure whether a second vascular event in the same patient will share the same components of the causal mechanism that led to the first. Moreover, we have no convincing evidence that changing therapy is a more effective strategy than maintaining an evidence-based antiplatelet regimen. Increased awareness of factors that may in-
terfere with the desired antiplatelet effects of aspirin or clopidogrel, particularly avoidable drug interactions, may result in better patient care than requesting unnecessary tests of platelet function. In fact, no test of platelet function is currently recommended to assess the antiplatelet effects of aspirin or clopidogrel in individual patients.

Efficacy and Safety of Low-Dose Aspirin in the Prevention and Treatment of Atherothrombosis in High-Risk Patients

The efficacy and safety of aspirin have been evaluated in several populations, ranging from apparently healthy persons at low risk to patients presenting with an acute myocardial infarction or an acute ischemic stroke. Among patients with occlusive vascular disease, both individual studies and a meta-analysis of trials of antiplatelet therapy indicate that aspirin and other antiplatelet drugs reduce the risk of a serious vascular event (nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes) by approximately 25 percent. This figure represents a composite of a 34 percent reduction in the rate of nonfatal myocardial infarction, a 25 percent reduction in the rate of nonfatal stroke, and a reduction by one sixth in the rate of death from a vascular or unknown cause. Since each of these proportional reductions applies similarly to all categories of patients with vascular disease, the absolute benefits of aspirin in individual patients can be estimated by reducing the estimated absolute risk of nonfatal myocardial infarction by one third, the risk of nonfatal stroke by one fourth, and the risk of death from vascular causes by one sixth. Thus, among a wide range of patients with vascular disease, in whom the annual risk of a serious vascular event ranges from 4 to 8 percent, aspirin typically prevents at least 10 to 20 fatal and nonfatal vascular events for every 1000 patients treated for one year (Fig. 3).

Observational studies and a meta-analysis of randomized clinical trials in high-risk patients have demonstrated that long-term therapy with low-dose aspirin approximately doubles the risk of major extracranial (mostly, upper gastrointestinal) bleeding. In middle-aged patients, this corresponds to an estimated absolute excess of approximately 1 to 2 major bleeding complications per 1000 patients treated with low-dose aspirin for one year. Moreover, there is an absolute excess of hemorrhagic strokes of 1 to 2 per 10,000 patients. Therefore, for most high-risk patients taking low-dose aspirin, the number in which a serious vascular event would be avoided clearly outweighs the number with a major bleeding episode, unless a given patient has increased susceptibility to bleeding owing to advanced age, a history of ulcer, or concomitant treatment with other drugs interfering

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**Figure 3.** Absolute Effects of Antiplatelet Therapy with Aspirin on the Risk of Vascular Events (Nonfatal Myocardial Infarction, Nonfatal Stroke, or Death from Vascular Causes) in Five Groups of High-Risk Patients.

The figure is based on an analysis of data from the Antithrombotic Trialists’ Collaboration.
with primary hemostasis or gastrointestinal cytoprotection.

Such a favorable risk–benefit ratio of low-dose aspirin in high-risk patients has resulted in level 1 recommendations, and the Food and Drug Administration has approved aspirin for patients at high risk for occlusive vascular disease. Despite such a recommendation, aspirin use appears to be less than optimal, according to cardiovascular registries and a recent survey. A history of adverse reactions to aspirin is a common reason for avoiding long-term use in high-risk patients. In a double-blind, placebo-controlled, randomized study of 150 patients using low-dose (80 mg daily) aspirin with upper gastrointestinal symptoms, treatment with a proton-pump inhibitor significantly reduced the rate of heartburn, but not other aspirin-related symptoms. In addition to causing gastrointestinal intolerance, aspirin is an infrequent cause of unpredictable hypersensitivity reactions, often referred to as “aspirin allergy.” Proper classification of patients who are allergic to aspirin and early referral of such patients to allergy services for potential desensitization may allow continued use of this lifesaving drug.

Thus, aspirin is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable risk–benefit profile. Given the potential of aspirin to cause dose-dependent impairment of gastric cytoprotection and endothelial thromboresistance, physicians are encouraged to use the lowest dose of aspirin shown to be effective in each clinical setting (Table 1). The available evidence supports the use of daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients. The use of a once-a-day regimen is preferable to the use of an every-other-day regimen because of interindividual variability in the platelet turnover rate, which represents an important determinant of the extent and duration of platelet inhibition on repeated dosing with low-dose aspirin. In clinical settings in which an immediate antithrombotic effect is required (such as in the presence of acute coronary syndromes or acute ischemic stroke), a loading dose of 160 to 200 mg should be given at the time of diagnosis to ensure rapid and complete inhibition of thromboxane-dependent platelet aggregation.

**Efficacy and Safety of Low-Dose Aspirin in Low-Risk Subjects**

In contrast to the clear benefits of low-dose aspirin on the risk of myocardial infarction, stroke, and death from vascular causes among high-risk patients with known occlusive vascular disease, its effects in low-risk persons are less clear. A meta-analysis of five primary-prevention trials indicated that aspirin reduces the risk of myocardial infarction by approximately 30 percent (which is similar to the benefit associated with secondary prevention) but has no significant effect on the risk of stroke. More recently, the results of the aspirin component of the Women’s Health Study, which compared 100 mg of aspirin every other day with placebo in approximately 40,000 apparently healthy women, were reported. The results were surprising because they appeared to contrast with the results of earlier trials, in which the majority of participants had been men. Aspirin reduced the risk of stroke by 17 percent (95 percent confidence interval, 1 to 31 percent; P=0.04), but there was no significant reduction in the risk of myocardial infarction (relative risk, 1.02; 95 percent confidence interval, 0.84 to 1.25). However, in secondary-prevention trials, the effects of aspirin on the risk of major coronary events and strokes were similar in men and women. The reasons for this apparent discrepancy remain unclear, and further research is needed to clarify this issue.

Whereas the benefits of aspirin exceed the risks of bleeding in most patients with clinically overt arterial disease, the risk–benefit ratio is marginal in low-risk populations. As shown in Figure 4, whereas the risk of a vascular event was almost 4 percent per year among patients with ischemic heart disease in the Swedish Angina Pectoris Aspirin Trial, such a recommendation, aspirin use appears to be less than optimal, according to cardiovascular registries and a recent survey. A history of adverse reactions to aspirin is a common reason for avoiding long-term use in high-risk patients. In a double-blind, placebo-controlled, randomized study of 150 patients using low-dose (80 mg daily) aspirin with upper gastrointestinal symptoms, treatment with a proton-pump inhibitor significantly reduced the rate of heartburn, but not other aspirin-related symptoms. In addition to causing gastrointestinal intolerance, aspirin is an infrequent cause of unpredictable hypersensitivity reactions, often referred to as “aspirin allergy.” Proper classification of patients who are allergic to aspirin and early referral of such patients to allergy services for potential desensitization may allow continued use of this lifesaving drug.

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### Table 1. High-Risk Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Daily Dose

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lowest Effective Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic stable angina</td>
<td>75</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>100</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>75</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>160</td>
</tr>
<tr>
<td>Transient ischemic attack and ischemic stroke</td>
<td>50</td>
</tr>
<tr>
<td>Severe carotid artery stenosis</td>
<td>75</td>
</tr>
<tr>
<td>Acute ischemic stroke</td>
<td>160</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>325</td>
</tr>
</tbody>
</table>

* The lowest effective daily dose is the lowest daily aspirin dose for which direct randomized evidence of effectiveness is available.
The average annual risk was much lower (0.3 to 1.6 percent per year) in six primary-prevention trials involving mostly asymptomatic subjects. The benefit of aspirin did not clearly outweigh the harm within this range of cardiovascular risk. In these primary-prevention trials, few subjects exceeded the threshold for aspirin prophylaxis recommended by the American Heart Association — a risk of coronary heart disease of 1 percent per year. It is worth remembering that these trials included few people older than 70 years of age, in whom the predicted risk of coronary heart disease and stroke rises steeply and who are the dominant demographic group at elevated risk (i.e., the risk exceeds 1 percent per year). The lack of randomized trials involving older people makes it difficult to assess whether any possible benefits of aspirin would exceed the known risks of upper gastrointestinal bleeding in this age group. As illustrated in Figure 5, the risk of such complications increases sharply among people 70 years of age or older. This risk is further increased by a history of gastrointestinal disturbances (Fig. 5) and by concomitant use of nonsteroidal anti-inflammatory drugs (data not shown). Although there seems to be a general agreement among gastroenterologists that proton-pump inhibitors should be prescribed to high-risk patients taking low-dose aspirin, such a strategy has not been widely adopted because of a lack of definitive evidence to support it.

**Figure 4. Benefits and Risks of Low-Dose Aspirin in Primary-Prevention Trials.**
The numbers of vascular events avoided and episodes of major bleeding caused per 1000 patients treated with aspirin per year are plotted from the results of individual placebo-controlled trials of aspirin in different patient populations characterized by various degrees of cardiovascular risk, as noted on the abscissa. WHS denotes Women’s Health Study, PHS Physicians’ Health Study, PPP Primary Prevention Project, HOT Hypertension Optimal Treatment Study, BDT British Doctors Trial, TPT Thrombosis Prevention Trial, and SAPAT Swedish Angina Pectoris Aspirin Trial. Data are modified from Patrono et al.60

**Future Directions**
There are several potential strategies for improving the ability of antiplatelet therapy to prevent atherothrombosis. One important aim is to ensure the appropriately wide use of aspirin (or some other effective antiplatelet regimen) among high-risk patients with vascular disease. Several surveys have indicated that many patients who may benefit do not routinely receive low-dose aspirin; considerable efforts are needed to improve these statistics. In some groups of patients, however, low rates of aspirin use reflect the lack of convincing evidence of its efficacy and safety; thus, there is a need for additional placebo-controlled trials in these groups. For example, the ongoing A Study of Cardiovascular Events in Diabetes should provide valuable information about the efficacy and safety of aspirin in people with diabetes with no history of vascular
events, and the Aspirin in Reducing Events in the Elderly study should provide such information about patients older than 70 years of age.

In high-risk patients who are already taking aspirin, it is reasonable to ask whether an alternative antithrombotic regimen might be more effective than aspirin. Although clopidogrel may be marginally more effective than aspirin in certain high-risk groups, adding a second antithrombotic agent (either an antiplatelet or an anticoagulant) to aspirin is likely to result in much larger reductions in risk than switching from aspirin to an alternative agent. Although there is already some evidence from randomized trials to support the use of this strategy, more information is needed on its efficacy and safety in different high-risk groups.

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We are indebted to Dr. Angel Lanas for reviewing and discussing several aspects of this article, to Dr. Patricia Kearney for assistance with the analyses included in Figure 3, to Dr. Roberto Marchioli for drafting the original version of Figure 4, and to Daniela Basilico for editorial assistance.

**REFERENCES**

A 71-YEAR-OLD MAN WAS EVALUATED FOR SEVERE ANEMIA (HEMOGLOBIN level, 7.1 g per deciliter; mean corpuscular volume, 106 µm³), extensive ecchymosis of the lower limbs (Panel A), gingivitis, and hemorrhages of the oral cavity (Panel B, arrows). There was no history of recent trauma. What is the diagnosis?

Editor’s note: We invite our readers to submit their answers at www.nejm.org/mystery. We will publish the diagnosis in the Correspondence section of the January 26, 2006, issue and e-mail it to everyone who submits an answer. All answers must be received by December 15, 2005.

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A Hole in the Argument

Donald D. Hegland, M.D., Geoffrey A. Kunz, M.D., J. Kevin Harrison, M.D., and Andrew Wang, M.D.

An 80-year-old man presented to his physician’s office for evaluation of shortness of breath and fatigue four weeks after repair of a hiatal hernia. He reported a mild, non-productive cough and abdominal bloating. Prior to the surgery, he had been very active and had had no dyspnea.

Postoperative shortness of breath may be due to many conditions, including atelectasis, pulmonary embolism, pneumonia, pneumothorax, cardiac arrhythmia, myocardial ischemia, heart failure, or even anemia. The absence of preoperative symptoms suggests that surgery was the precipitating event. Given the type of surgery performed, one possible sequela is bronchospasm due to gastroesophageal reflux.

The patient had a history of hypertension, hypercholesterolemia, and osteoarthritis. Ten years earlier, he had undergone percutaneous coronary intervention for angina and single-vessel coronary artery disease. He had undergone laparoscopic fundoplication for gastroesophageal reflux and hiatal hernia seven years before the current problem, but required repeated fundoplication four weeks before he reported his current symptoms. Before his recent fundoplication, a stress test with myocardial perfusion imaging was performed. The patient exercised for 4 minutes 50 seconds and attained a maximum heart rate of 140 beats per minute without symptoms or electrocardiographic abnormalities. The perfusion images showed no evidence of ischemia. This patient’s preoperative medications included aspirin, isosorbide mononitrate, atenolol, and simvastatin, which were unchanged after the surgery.

There was no history suggestive of pulmonary disease. Although the patient does have a history of coronary artery disease, his preoperative stress test demonstrated a good functional capacity, and there was no evidence of myocardial ischemia.

On physical examination, the patient appeared younger than his chronologic age and he was not in distress. His blood pressure was 103/61 mm Hg, heart rate 66 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 82 percent. His weight was 84 kg and height 173 cm (body-mass index [the weight in kilograms divided by the square of the height in meters], 28.1). His sclerae were anicteric. His lungs were clear on auscultation. The jugular venous pressure and heart sounds were normal, without murmur, gallop, or rub. There was no evidence of hepatosplenomegaly or ascites. There was mild (1+) bilateral edema below the knees and mild cyanosis of the lips and nail beds, but no clubbing was evident. The remainder of his physical examination was normal.
The patient was found to have a substantial reduction in arterial oxygen saturation, with unremarkable findings on physical examination. The normal cardiac examination and clear lung fields suggest that heart failure or significant pulmonary parenchymal disease is unlikely to explain his dyspnea. I am particularly worried about pulmonary embolism, especially given the onset of symptoms after surgery. Methemoglobinemia may occur in patients taking nitrates (particularly with very high doses or additional oxidant stresses) and may cause arterial oxygen desaturation. However, isosorbide mononitrate was not a newly prescribed medication, and the risk of clinically important methemoglobinemia with long-term nitrate use is low.

The white-cell count was 4700 per cubic millimeter, the hemoglobin level 13.7 g per deciliter, and the platelet count 199,000 per cubic millimeter. The levels of serum electrolytes were normal. Levels of hepatic transaminases, serum alkaline phosphatase, bilirubin, total protein, and albumin were normal. The level of B-type natriuretic peptide was 117 pg per milliliter (normal range, 0 to 100). Arterial blood gas values obtained while the patient was breathing room air revealed a pH of 7.49, a partial pressure of carbon dioxide of 35 mm Hg, a partial pressure of oxygen of 35 mm Hg, a bicarbonate level of 27 mmol per liter, and an oxygen saturation of 73 percent. While the patient was breathing pure oxygen by face mask, arterial blood gas values included a pH of 7.45, a partial pressure of carbon dioxide of 35 mm Hg, a partial pressure of oxygen of 44 mm Hg, a bicarbonate level of 25 mmol per liter, and an oxygen saturation of 82 percent. Measurement of blood gases with co-oximetry demonstrated a normal methemoglobin level of 0.6 percent. A chest radiograph (Fig. 1) showed an enlarged cardiac silhouette and a tortuous descending aorta, but there was no evidence of pulmonary infiltrate or edema. An electrocardiogram showed sinus rhythm.

The absence of erythrocytosis is consistent with the subacute duration of the patient’s hypoxemia. The fact that his severe hypoxemia did not improve with the administration of pure oxygen suggests the presence of right-to-left “shunt physiology.” The refractoriness of shunt-related hypoxemia to treatment with inhaled oxygen is attributable to the transit of deoxygenated blood directly into normally oxygenated blood, without oxygen uptake in the pulmonary capillaries. In addition to pulmonary embolism, causes of right-to-left shunting of blood include other intrapulmonary shunts (for example, arteriovenous malformations) as well as intracardiac conditions (e.g., atrial or ventricular septal defects), or extracardiac conditions (patent ductus arteriosus with severe pulmonary hypertension).

Computed tomography (CT) of the chest with the administration of intravenous contrast material showed no evidence of pulmonary emboli or pulmonary arteriovenous malformations. The ascending aorta and proximal descending thoracic aorta were mildly dilated. The esophagus appeared mildly distended with fluid and gas. A high-resolution CT scan of the chest showed mild scarring in the right lung without infiltrate or pleural effusion. A transthoracic echocardiogram showed normal size and function of both the left and right ventricles. There was mild mitral-valve and tricuspid-valve regurgitation; estimated pulmonary-artery systolic pressure was 30 mm Hg, based on the velocity of the tricuspid regurgitation jet. No intracardiac shunt was evident with the use of two-dimensional or color Doppler flow imaging. Pulmonary-function tests demonstrated normal spirometry, lung volumes, and diffusion capacity of carbon monoxide.

A sleep study revealed a total of 80 obstructive apneic episodes, 13 central apneic episodes, 7 mixed apneic episodes, and 23 hypopneic episodes (apnea–hypopnea index of 21 events per hour).
The baseline oxygen saturation was 91 percent, and the lowest recorded saturation value during sleep was 77 percent. Continuous positive airway pressure (CPAP) at 9 cm of water reduced the apnea–hypopnea index to 2.6 events per hour, and the minimal oxygen saturation increased to 89 percent. The patient was prescribed home oxygen therapy and CPAP by nasal mask when sleeping.

Although the findings meet the criteria for the diagnosis of moderate obstructive sleep apnea (15 to 30 apneic–hypopneic events per hour of sleep), this diagnosis does not adequately explain the patient’s dyspnea and hypoxemia. Chronic hypoventilation syndromes, such as the obesity–hypoventilation syndrome, may be associated with hypoxemia, but the normal values for partial pressure of carbon dioxide measured in prior arterial blood gas tests do not support hypoventilation as the cause of his hypoxemia.

The patient underwent a cardiac catheterization for evaluation of persistent hypoxemia, which revealed a right atrial pressure of 3 mm Hg, a right ventricular pressure of 25/5 mm Hg, a pulmonary artery pressure of 25/10 mm Hg (mean pressure, 15 mm Hg), a pulmonary-capillary wedge pressure of 5 mm Hg, a left-ventricular systolic pressure and an end-diastolic pressure of 125 and 8 mm Hg, respectively, and an aortic pressure of 125/80 mm Hg. Left ventriculography revealed an ejection fraction of 60 percent, without mitral regurgitation or ventricular septal defect. The results of coronary angiography were normal. Oximetry data obtained with the patient breathing room air showed the following oxygen-saturation values: inferior vena cava, 70 percent (normal, 65 to 87 percent); superior vena cava, 68 percent (normal, 67 to 83 percent); right atrium, 69 percent (normal, 65 to 87 percent); right ventricle, 65 percent (normal, 67 to 84 percent); pulmonary artery, 65 percent (normal, 67 to 84 percent); pulmonary-capillary wedge pressure, 88 percent (normal left atrial saturation, 92 to 98 percent); left ventricular, 93 percent (normal, 92 to 98 percent); and descending aortic, 89 percent (normal, 92 to 98 percent). The decrease in oxygen saturation between the left ventricle and the descending aorta prompted concern for a possible extracardiac right-to-left shunt. However, a magnetic resonance imaging (MRI) scan with angiography showed no evidence of an intrathoracic right-to-left shunt.

The oximetric measurements obtained during cardiac catheterization may suggest the presence and location of a shunt, apparent as a decrement in oxygen saturation at a site in the pulmonary venous or systemic arterial circulation. Measurement of the partial pressure of oxygen may be more sensitive than measurement of oxygen saturation, since hemoglobin saturation is preserved over a wide range of values for oxygen partial pressure.

The patient’s oximetric results are difficult to interpret. The pulmonary-capillary wedge oxygen saturation was measured as a surrogate for the pulmonary venous saturation to differentiate between a pulmonary shunt (low pulmonary venous saturation) and a cardiac shunt (normal pulmonary venous saturation). However, if the catheter is not occlusive, this sample may be partially diluted by pulmonary arterial (mixed venous) blood, resulting in a falsely low estimate of the true pulmonary venous oxygen content. This contamination is suggested by the fact that the left ventricular oxygen saturation is higher than that of the pulmonary-capillary wedge saturation.

The decrement in oxygen saturation from the left ventricle to the femoral artery probably reflects variability in the measurement of oxygen saturation. A systemic venous-to-arterial shunt is not a likely finding because the normal right heart and pulmonary arterial pressures are much lower than systemic arterial pressure.

The patient was referred to our institution for evaluation of hypoxemia. On examination, his oxygen saturation was found to be 94 percent when he was in the supine position and 76 percent in the standing position.

This finding of orthodeoxia, a decrease in arterial oxygen saturation from the recumbent to the erect position, may occur with a number of conditions, including recurrent pulmonary emboli, chronic lung disease, liver disease (specifically, hepatopulmonary syndrome), previous pneumonectomy, pulmonary arteriovenous malformations, and patent foramen ovale. Most of the potential causes have been ruled out in this patient on the basis of previous testing, but the possible presence of a patent foramen ovale has not been adequately evaluated.

Transthoracic echocardiography was repeated with an intravenous injection of agitated saline in both the supine and standing positions. This demon-
strated minimal shunting of microbubbles in the supine position, but significant opacification of the left atrium and ventricle by microbubbles when the patient was standing (Fig. 2; and Video Clips 1 and 2 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). A transesophageal echocardiogram confirmed the presence of a patent foramen ovale, with markedly increased right-to-left shunting across the foramen ovale when the patient was in the sitting position (Fig. 3).

Contrast injection during echocardiography may be used to evaluate the presence of a right-to-left shunt. Upon transit to the right heart of the agitated saline bolus, which has increased echogenicity because of the creation of microbubbles, the right atrium and right ventricle are filled with this contrast solution. In the absence of a shunt, these small bubbles are trapped in the pulmonary capillaries and gradually dissipate without being visualized in the left heart chambers. Visualization of microbubbles in the left heart within a few cardiac cycles of their opacification of the right heart chambers suggests the presence of an intracardiac shunt, whereas their delayed appearance in the left heart suggests an intrapulmonary shunt.

Review of the operative note from the recent fundoplication revealed that the hiatal hernia was densely adherent in the mediastinum and that the fundoplication was secured in the abdomen by sutures to the preaortic fascia.

Mobilization of the stomach out of the mediastinum and retraction of the fundoplication may have contributed to the dynamic alteration of atrial geometry and the patency of the foramen ovale in the upright position.

The patient underwent percutaneous closure of the patent foramen ovale in the cardiac catheterization laboratory with implantation of a septal defect occlusion device without complication. At a three-month follow-up, he no longer experienced shortness of breath. His oxygen saturation while breathing room air was 98 percent in the supine position and 97 percent when standing.

**COMMENTARY**

An understanding of pathophysiology often guides the formulation of a differential diagnosis. Findings from the patient’s evaluation may then be used to support or refute proposed diagnoses. In this case, the clinicians recognized correctly that the hypoxemia was due to a shunt, and an appropriate differential diagnosis was formulated. However, the intermittent, positional nature of shunting through the patent foramen ovale obscured its detection. Oxygen saturation measurements that were made intraoperatively and postoperatively were likely performed with the patient supine, as were subsequent measurements in the cardiac catheterization laboratory. These measurements demonstrated no or mild hypoxemia, in contrast to the measurements that were obtained during other evaluations.

Orthodeoxia may be accompanied by the symptom of platypnea, the sensation of difficulty in breathing when erect that is relieved by recumbency...
(a condition termed the platypnea–orthodeoxia syndrome). When present, the platypnea–orthodeoxia syndrome is usually caused by a patent foramen ovale, intrapulmonary vascular shunt, or severe ventilation-perfusion mismatching and should be considered when hypoxemia is positional or more pronounced than expected on the basis of cardiac and pulmonary findings.

From a physiological perspective, the confirmation, localization, and quantification of a shunt is most accurately performed by direct measurement of oxygen content at distinct sites throughout the cardiopulmonary system. However, such an oximetry series, often termed a shunt run, involves an invasive procedure. Furthermore, differentiating between a pulmonary cause and a cardiac cause of hypoxemia requires measurement of the oxygen content at the site where it is expected to be highest (in the pulmonary veins); this site may not be readily accessible in the absence of an atrial septal defect or without performing a transseptal catheterization.

Alternatively, a shunt may be diagnosed by imaging methods. Abnormalities of the pulmonary vasculature, such as pulmonary embolism or arteriovenous malformations, may be visualized by angiography during CT or MRI. Transthoracic echocardiography is highly sensitive for the presence of a ventricular septal defect, but may not clearly visualize the atrial septum because of its posterior location in the thorax. If an atrial septal defect or a patent foramen ovale is strongly suspected, a transesophageal echocardiogram is more sensitive and more likely to detect it. As described above, intravenous injection of contrast media during echocardiography may disclose the presence of a shunt and demonstrate whether a shunt is dynamic or positional in nature. The sensitivity of this technique may be augmented by having the patient cough or perform a Valsalva maneuver, thereby increasing intrathoracic pressure and right-to-left shunting. Right-to-left shunting may thus be detected through small defects, such as a patent foramen ovale, even in the setting of normal right heart pressures.

Although it was a congenital heart defect, the patient’s patent foramen ovale was not clinically apparent for 80 years. Furthermore, a patent foramen ovale is typically associated with no or minimal left-to-right shunting, and the development of right-to-left shunting was an acquired element of this anomaly. The platypnea–orthodeoxia syndrome due to a patent foramen ovale is often triggered by an intercurrent event or condition, such as aortic dilation, pulmonary embolus, pneumonectomy, or diaphragmatic paralysis. The acute onset of orthodeoxia in this patient cannot be attributed to a change in aortic dimensions in the absence of a dissection. Right-to-left shunting may result from elevated right heart pressures, such as might occur in the setting of a pulmonary embolus, but his right heart pressures were normal. A perioperative myocardial infarction involving the right ventricle may also lead to an acute elevation of right atrial pressure, but the right ventricle would have appeared dilated and hypococontractile on echocardiography. As theorized above, alteration of atrial geometry by the fundoplication may have resulted in a positional increase in the patency of and shunting through the patent foramen ovale.

This case also highlights the challenge of determining the clinical significance of a common
anomaly. A patent foramen ovale is reported to be present in at least 10 percent of the general population. Although the majority of these findings are not clinically significant, a patent foramen ovale may be associated with important sequelae, including paradoxical embolism (with subsequent cerebrovascular accident) and hypoxemia, as illustrated in this case. Because of the high prevalence of the condition, an increased rate of detection by echocardiography, and the potential for percutaneous closure, careful consideration of the significance of a patent foramen ovale is important in clinical decision making, as described by Kizer and Devereux in this issue of the Journal. When confronted with such a puzzle, searching for holes in the data may allow the clinician to refine the diagnostic possibilities and ultimately to identify the underlying problem.

REFERENCES


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Many arguments have been raised over the years to justify not moving rapidly forward with anti-retroviral treatment programs for people living with the human immunodeficiency virus (HIV) and AIDS in settings with limited resources. The standard litany included the price of therapy as compared with the poverty of the patient, the complexity of the intervention, the lack of infrastructure for laboratory monitoring, and the staggering lack of trained health care providers. Narrow cost-effectiveness arguments have been commonplace. False dichotomies — prevention or treatment, rather than both — have too often gone unchallenged. Perhaps of greatest concern several years ago was the ambivalence — if not the silence — of political leaders and experts in public health. The cumulative effect was to allow the death of tens of millions of poor people in developing countries who are living with and becoming ill as a result of HIV infection. Meanwhile, in countries rich in resources, HIV infection has largely become a manageable, chronic condition because of the availability of combination-drug antiretroviral treatment.

The inequity between rich and poor countries in terms of access to HIV treatment has rightly given rise to widespread moral indignation, and a few outstanding leaders have been consistent and courageous in their personal and public stances. The national program in Brazil has long shown what can be achieved when there is unswerving political commitment and public health leadership. Some innovative projects pioneered by international nongovernmental organizations in diverse settings have clearly established that a very simple approach to antiretroviral treatment with intensive community engagement and support can achieve remarkable results. In 2000, the United Nations Accelerating Access Initiative finally brought the research-based pharmaceutical industry into play and, with the rise in generic competition, drug prices have since fallen substantially. At the same time, fixed-dose combinations have become more widely available.

Building on these lessons, the World Health Organization (WHO) has advocated a public health approach for treating people with HIV and AIDS in resource-limited settings. This approach proposes the use of standard first-line treatment regimens based on a simple five-drug formulary, with a more complex — and so far, much more expensive — set of second-line options. The steps in decision making for patients (the mnemonic is “the four S’s”: when to start, substitute for toxicity, switch for failure, or stop and move to end-of-life care) have been standardized, and intensive-training packages for health and community workers have been developed and implemented in many countries.

These rapid advances in public health have been matched by unprecedented opportunities and funding through the President’s Emergency Plan for AIDS Relief (PEPFAR) in the United States, The World Bank, and the Global Fund to Fight AIDS, Tuberculosis and Malaria. In 2003, the lack of access to treatment was declared a global public health emergency by the WHO and the Joint United Nations Programme on HIV and AIDS (UNAIDS), and the two agencies launched the “3 by 5” initiative, with the ambitious, aspirational target of having 3 million people receiving antiretroviral therapy in developing countries by the end of 2005. Many countries have since set corresponding national targets and worked gallantly to embed treatment within their own national AIDS programs and health systems and to harness the synergistic connections between treatment for HIV and AIDS and preventive inter-
ventions. The recent communiqué from the Group of Eight, more commonly known as G8, endorsing universal access to HIV treatment by 2010 is another major step forward.

These encouraging advances mean that there can be no more excuses for not expanding global access to antiretroviral treatment. Solid progress has been made — with approximately 1 million people estimated to have been in treatment by June 2005 — although not at the desired pace.9

Certainly, significant challenges remain. Some skeptics doubt that a high standard of care can be provided by nurses and community health workers (rather than scarce highly trained physicians10), although this approach is now being used successfully in many countries. But we who have worked in developing countries know that in many settings that are poor in resources, adoption of a decentralized model of care is essential if health systems are to overcome serious human-resource constraints and move toward the goal of monitoring and supporting patients for life. Innovative strategies to support adherence may be required, but so far, adherence rates in even the most impoverished settings compare favorably with those of patients in the United States.11 Drug-supply links are fragile in many countries, but concerted efforts are now being made to strengthen them, with potentially great benefits for the provision of other essential medicines. It is now clear that responding aggressively to HIV and AIDS is critical to reinforcing health systems as a whole and to achieving broader development objectives in the coming decade.12

The article by Severe et al. from the Groupe Haïtien d’Étude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) project in this issue of the Journal13 is particularly important for the contribution it makes to the still-limited published literature on the scale-up of access to antiretroviral therapy in settings with limited resources. Port-au-Prince, Haiti, is one of the most challenging urban centers in the world in which to implement a major public health intervention. The results, as compared with those from settings in the United States, are truly remarkable. In a setting with only limited infrastructure and few staff members, over 1000 patients are now being treated. After one year of therapy, 87 percent of adults and 98 percent of children were still alive. Dropout rates were less than 8 percent, an outcome that vindicates the decision to link the treatment program with nutritional supplementation and existing social programs. Of particular note is the estimated cost per patient in treatment per year: about $1,600 with (largely generic) antiretroviral medications accounting for 35 to 40 percent of the total.

What are the tasks ahead for those of us working in these programs? In most countries where there is a high prevalence of infection with HIV and AIDS, the number of people in need of treatment still exceeds the capacity to provide it. Enrollment must be accelerated in both urban and rural settings, and sufficient quantities of good-quality, affordable antiretroviral medicines must be guaranteed. In the years ahead, keeping patients on treatment will be by far the greatest challenge, and information about evidence-based approaches and best-practice protocols for the management of chronic diseases in settings with limited resources is sorely needed. Adherence support, rather than regimen potency, may be the single most critical determinant of long-term success. Our overall efforts to combat the epidemic of HIV and AIDS must build on the pace and rhythm that countries have achieved already in their responses to the concrete treatment goals set first by PEPFAR and then by the WHO with the 3 by 5 initiative. Most important, we must bring a rapidly accelerated pace to our prevention efforts. We must move beyond pilot projects, set clear prevention targets that are time-limited, and dramatically accelerate our efforts in testing and counseling. The recent commitment from the minister of health in Lesotho to offer an HIV test to every person in his country in short order could build much-needed momentum and provide an example that should be replicated in other high HIV-burden settings.

It has often been said that our generation will be judged by our response to the HIV and AIDS pandemic. Although there is much more to do, the GHESKIO project and the responses from many other developing countries give us hope that the final judgment may be less harsh than we had feared.

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In comparing current clinical outcomes in renal transplantation with those of 30 years ago, graft failure from immunologic factors and death from opportunistic infection in the first year after transplantation are no longer common clinical outcomes. The therapeutic regimens used today to prevent and treat rejection or infection among renal-transplant recipients bear only a small resemblance to those used 30 years ago.

In contrast, the diagnostic strategies used to detect rejection and distinguish it from other causes of renal dysfunction have not budged during the past two decades. A rise in the level of serum creatinine suggests allograft dysfunction, but the reasons can be elusive. Nephrotoxicity from immunosuppressive agents may cause acute and chronic allograft dysfunction, and accordingly, clinicians attempt to maintain drug levels in the therapeutic range. To aid in the resolution of the difficult differential diagnosis of allograft dysfunction, ultrasonography and renal biopsy are often performed.

This reactive diagnostic approach is often too late, and there are limitations because, first, drug levels do not test how therapy is affecting the recipient’s immune response, and second, biopsies lack sensitive histologic patterns for the diagnosis of drug-induced nephrotoxicity and early rejection. Furthermore, detecting adverse host antigen receptor infiltration before there is evidence of graft dysfunction has not been feasible. Since the diagnosis of rejection is made after the advent of renal damage, it is not surprising that the necessarily late application of antirejection therapy often results in only partial restoration of renal-transplant function. Serial surveillance biopsies of the transplant, a maneuver that would undoubtedly detect some instances of subclinical rejection, are precluded by cost and complication-related issues.

The advent of reverse transcriptase polymerase chain reaction and DNA-microarray technology has allowed for highly sensitive, accurate, and quantitative detection of the transcriptional profiles of tissue samples from recipients and donors, thereby enabling the discovery of a molecular signature for acute cellular rejection. Acute allograft rejection is characterized by infiltration of the allograft by activated T cells. Accordingly, expression of T-cell–activation genes is evident in renal-transplant biopsy specimens obtained from patients who are undergoing transplant rejection. Knowing that activated donor-specific cytotoxic T lymphocytes (CTLs) infiltrate rejecting allografts, the expression of T-cell–activation genes that control the cytolytic machinery of activated CTLs was first analyzed in renal-transplant biopsy specimens.

Since the transplant is infiltrated by a T-cell–rich population of mononuclear leukocytes, robust intragraft expression of the T-cell–specific T-cell antigen receptor and T-cell–specific CD3 genes are excellent markers for rejection. Nonetheless, infiltration with other mononuclear leukocytes is also noted during rejection. Particularly interesting is the observation that amplified expression


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**Rejection — More Than the Eye Can See**

Terry B. Strom, M.D.
of the B-cell–specific CD20 gene in the context of robust expression of CTL-related genes and other activation genes provides a molecular signature for rejection episodes that are resistant to corticosteroid therapy.9

To enhance the use of transcriptional profiling methods, noninvasive techniques that do not rely on renal biopsy are desired. In fact, the molecular signature of rejection, amplified expression of CTL genes, can be detected in circulating blood cells at the time of rejection.10 A drawback to the use of circulating blood is that blood cannot be used to analyze the heterogeneous population of mononuclear leukocytes that infiltrate rejecting allografts. In contrast, under most circumstances, lymphocytes that are present in the urine of patients with renal transplants have traversed the kidney before entering the urine flow. A notable innovation of Suthanthiran and colleagues has been the clever use of urine-sediment cells for transcriptional profiling studies.8 Parallel studies comparing renal-transplant biopsy specimens and urine-sediment cells reveal a similar sensitivity and specificity of gene expression for CTL-effector molecules, CD3, and other genes for the diagnosis of rejection.8 In this issue of the Journal, the Suthanthiran group has extended these studies in the study by Muthukumar et al.,3 which reaffirms that amplified expression of CD3 (a T-cell-lineage–specific transcript), perforin (an activated CTL transcript), and CD25 (a T-cell–activation transcript) is far more robustly expressed in urine-sediment cells from renal-transplant recipients with acute rejection than in cells from patients with either chronic rejection or a normal biopsy.3

In addition, Muthukumar et al. have carefully studied FOXP3 gene expression. Expression of the FOXP3 gene, a member of the forkhead family of cell-differentiation genes, is a lineage-specific transcript for graft-protecting regulatory T cells.14 FOXP3 is the master switch that turns on the immunosuppressive properties of regulatory T cells.14 The finding that increased FOXP3 expression is a correlate of rejection is somewhat of a surprise. The molecular footprints for both cytopathic and protective cells are detected in T cells that have traversed the kidney and are collected from the urine sediment.3 Thus, the complex nature of immune response to the kidney transplant at the cellular level is made evident by the lineage-specific gene expression detected within urinary-sediment cells. Rejection is orchestrated by cytopathic, tissue-injuring CD4+ helper type 1 and CD8+ CTL T cells, but the study by Muthukumar et al. demonstrates that some FOXP3-positive protective T cells are also present within the graft during rejection.

The revelation in the new study is the remarkable ability of FOXP3 transcript levels to predict clinical outcomes. Although the molecular signature of rejection is present, low expression of FOXP3 at the time of rejection forewarns that rejection is severe and may not readily respond to antirejection therapy. Moreover, low expression of FOXP3 identifies transplants at heightened risk of graft failure within six months. Higher FOXP3 transcript levels at the time of rejection, despite the molecular signature of rejection, heralds a more favorable clinical outcome. It is notable that the histologic grade of rejection (Banff score) does not predict the severity or clinical outcome of treated rejection episodes. Why? Pathological examination of a transplant biopsy can measure the magnitude and scope of graft infiltration by leukocytes, but routine pathological analysis is not informative as to the cellular program (destructive or protective) of the graft-infiltrating cells.

In animal studies, therapeutic regimens that successfully induce donor-specific tolerance and thereby allow the safe withdrawal of immunosuppressive therapy serve to tip the balance of immunity from the predominant cytopathic-type antidonor immunity detected in untreated hosts toward the enduring ascendancy of protective-type immunity.15 The clinical data arising from the report of Muthukumar et al., taken together with experimental data, strengthen and add texture to the concept that the balance of cytopathic-type immunity to protective-type immunity determines both gross and subtle clinical outcomes, even in hosts receiving daily immunosuppressive therapy.

The potential for molecular diagnostic techniques to predict renal-transplant rejection, the safety of drug withdrawal, and other long-term and short-term outcomes may be substantial. The influence of assessing the molecular status of renal transplants in the operating room on later clinical outcome is also being analyzed.13 Overall, molecular diagnostic strategies are being tested in multicenter clinical trials sponsored by the National Institutes of Health and the Immune Tolerance Network. If the validity of these methods can be confirmed, the door to more effective...
and individualized therapy will be wide open. The present definition of “successful” treatment of a rejection episode is a loss of renal function of less than 15 percent. It would be a great improvement if the techniques described by Muthukumar et al. could lead to preemptive anticipation of problems and fully successful therapy.

Dr. Strom reports serving as a member of the Immune Tolerance Network.

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Applying Public Health Principles to the HIV Epidemic


Although human immunodeficiency virus (HIV) infection has killed more than half a million people in the United States, a comprehensive public health approach that has stopped other epidemics has not been used to address this one. When HIV infection first emerged among stigmatized populations (homosexual men, injection-drug users, and immigrants from developing countries), the discriminatory responses ranged from descriptions of AIDS as “retribution” to violence and proposals for quarantine, universal mandatory testing, and even tattooing of infected persons. This response led to HIV exceptionalism, an approach that advocated both for special resources and increased funding and against the application of standard methods of disease control. The need for extra resources remains essential, but the failure to apply standard disease-control methods undermines society’s ability and responsibility to control the epidemic.

Now, given the availability of drugs that can effectively treat HIV infection and progress on antidiscrimination initiatives, perhaps society is ready to adopt traditional disease-control principles and proven interventions that can identify infected persons, interrupt transmission, ensure treatment and case management, and monitor infection and control efforts throughout the population (Table 1). Doing so will have political and economic costs. The political costs include offending both sides of the political establishment: conservatives who oppose the implementation of effective prevention programs, including syringe exchange and the widespread availability of condoms, and some HIV activists who oppose expansion of testing, notification of the partners of infected persons, interrupt transmission, ensure treatment and case management, and monitor infection and control efforts throughout the population (Table 1). Doing so will have political and economic costs. The political costs include offending both sides of the political establishment: conservatives who oppose the implementation of effective prevention programs, including syringe exchange and the widespread availability of condoms, and some HIV activists who oppose expansion of testing, notification of the partners of infected persons (also known as partner counseling and referral services), and what some see as inappropriate “medicalization” of the response to the epidemic. The economic costs, particularly to improve population-wide case management and notification of partners, would be substantial. But the human and economic costs of failing to adopt a comprehensive public health approach are much higher.

We have identified and elucidated the biology of the virus, established and improved diagnostic tests, and created effective drugs and care systems that have reduced the number of deaths from AIDS in the United States by 70 percent since 1995. However, 25 years into the epidemic, progress is stalled. The number of deaths among people with AIDS has not declined since 1998, and the number of newly diagnosed cases is rising slightly. Disease transmission continues at the same or, possibly, a slightly higher rate. High-risk behavior remains common and is increasing in some groups. Late diagnosis of infection is common. Notification of the partners of infected persons is rare. Black and Latino patients are less likely than white patients to receive optimal care. Few patients in care receive counseling about preventing transmission of the virus. All these trends are apparent in New York City, which is home to one in six of all U.S. patients with AIDS.

When HIV testing became available 20 years ago in the absence of treatment and in the context of discrimination, the use of prescriptive regulations mandating counseling and separate written consent, based largely on the genetic-counseling model of testing for untreatable conditions, was reasonable. Today, the existence of these regulations and the separation of counseling and testing from routine medical care result in missed opportunities to diagnose, treat, and stop the spread of HIV infection. Nearly half of black men tested in public venues where men who have sex with men congregate (e.g., bars, bathhouses, and parks) in 2004...
and 2005 were HIV-positive, and two thirds of those who were positive were unaware of their status.\textsuperscript{7} Our outdated approach to HIV screening means that we not only fail to identify infected patients promptly and thus allow the epidemic to continue to spread, but we may also perpetuate HIV-related stigma by targeting screening only to those perceived to be at risk. Routine, voluntary HIV testing in health care settings, although advocated by the Centers for Disease Control and Prevention (CDC) for more than a decade,\textsuperscript{8} widely recommended,\textsuperscript{9} and cost-effective,\textsuperscript{10} has not occurred. In New York City in 2002, only one third of adults who had had three or more sex partners in the preceding year — and only half of men who had sex with men who had had three or more partners — had been tested for HIV in the previous 18 months.

| Table 1. Comparison of Public Health Approach to HIV Infection and Other Infectious Diseases. |
|-------------------------------------------------|---------------------------------------------------------------------|--------------------------|
| **Intervention**                                 | **Other Infectious Diseases**                                       | **HIV Infection**        |
| Case finding and surveillance                   | Named reporting of all with condition                               | Only recently implemented in many areas; still not implemented in some |
|                                                | Availability of routine testing in health care settings              | Widely recommended and cost-effective but often not available |
|                                                | Notification and testing of partners by public health programs       | Wide variation in proportion of contacts identified, contacted, and tested among jurisdictions |
| Interruption of transmission                    | Specific to mode of transmission                                    | Transfusion-related and perinatal transmission largely controlled in the United States; vaccines not available; condoms neither widely available nor use strongly promoted; use of nonsterile needles by most injection-drug users |
| Systematic treatment and case management        | Monitoring by public health agencies to determine whether infected contacts are receiving appropriate care and treatment | Generally not done |
|                                                | Case management by public health departments to ensure effective linkage of affected patients to care | Rarely done; duplication of services between community-based and government case management |
|                                                | Provision of social services to patients                             | Linkage of social services to care and treatment in few areas |
| Population-based monitoring                     | Contact of treating physicians by public health agencies if patients have inadequate response to treatment | Not done; treatment complex and lifelong |
|                                                | Monitoring of trends in drug resistance among previously untreated patients | Not routine except on a research basis (mandated recently in New York State) |
Early diagnosis is essential both to link patients to effective care and to prevent the spread of infection. The CDC estimates that more than half of new HIV infections are spread by HIV-positive people who are unaware they are infected.11 In nearly 40 percent of persons who received a diagnosis of HIV infection, AIDS either was concurrently diagnosed or developed within a year.3 They had been infected with HIV for about a decade; health care and other institutions missed many opportunities to diagnose their infection. As a result of delayed diagnosis, such patients are sicker when they begin to receive care and will thus die sooner than those whose infection is diagnosed promptly. Many unwittingly spread HIV to their spouses, partners, and others. Once they know their diagnosis, people infected with HIV reduce their practice of high-risk sex by about half,12 and the risk of heterosexual transmission, at least, is further reduced by treatment that decreases the viral load to below 1500 copies of HIV type 1 RNA per milliliter.13 Voluntary HIV screening and linkage to care should become a normal part of medical practice, similar to screening for other treatable conditions, such as high cholesterol levels, hypertension, diabetes, and breast cancer. Screening and linkage to care are especially important in communities with a high prevalence of HIV infection.

The partners of more than two thirds of people with newly diagnosed HIV infection do not receive organized partner notification, and when contact is attempted, the rate of success varies greatly.4 The notification of partners by public health counselors is more effective than notification by individual patients,14 but this approach is rare in most areas. As a result, most partners are not notified of their exposure or offered testing, contributing to late diagnosis and continued spread of HIV. Of 4312 persons with newly diagnosed HIV infection in New York City in 2003, information on these persons’ partners was available for less than a fifth and testing results were confirmed for fewer than 200 partners. In addition, the policy of offering partner notification only at the time of diagnosis ignores the continuing high-risk sexual behavior of many HIV-positive persons. Systematic notification of partners by public health personnel and the use of newer antibody or nucleic acid–amplification tests in addition to traditional methods could identify social networks and acute or early HIV infections and could potentially stop clusters of transmission.

The application of the public health principles of near-universal screening and treatment has all but eliminated transfusion-related and perinatal transmission of HIV.3 Among injection-drug users, syringe-exchange programs and widespread voluntary screening for the virus reduced the rate of transmission by 50 to 80 percent.15 Further progress in preventing HIV infection is possible — interventions to change behavior work16-19 — but reducing sexual transmission is challenging. Evidence-based ways to reduce high-risk behavior include promoting the use of condoms and making free condoms widely available,16,19 including in schools20; making clean needles readily available to people who inject illicit drugs21; and community interventions.19

Condoms, which can substantially reduce transmission,16,22 are not widely available nor is their use strongly promoted, and they are still used infrequently in high-risk sexual encounters.23 Most injection-drug users in the United States continue to use nonsterile needles.24 Until recently in New York City, condom-distribution programs were limited, even in high-risk settings, and several neighborhoods in need of syringe-exchange services were not served by these programs.
and clean needles, and treatment for substance abuse and mental health conditions, would improve individual treatment outcomes and reduce disease transmission, but it is uncommon.

Case management is prominent in the HIV service delivery system, yet few if any jurisdictions ensure that every patient is offered effective treatment and prevention services. Public health interventions to monitor and improve HIV case management can be effective but are rare.

**Case management**

It took nearly two decades to make HIV reportable throughout the United States, and named reporting is still not universal. Although information on CD4 cell counts and viral loads is collected in most jurisdictions, monitoring these data to determine patients’ progress is rare. Surveillance for drug-resistant strains of virus in patients who have never been treated is generally not conducted. Information on viral loads, CD4 cell counts, and drug resistance recently became reportable in New York State, thus making it possible to identify patients who are not receiving effective care, monitor trends in drug resistance, potentially identify clusters of disease, and potentially provide physicians and their patients who are not receiving care with more intensive services. Publicly funded case management, treatment, and service systems are not effectively coordinated to ensure a continuum of care. Effective population-based monitoring and evaluation would track not only the incidence, prevalence, and mortality of HIV infection, but also indicators of the interruption of transmission, such as the use of voluntary testing, proportion of partners notified, linkage to care of those who test positive, and success at reducing viral load when treatment is clinically indicated.

The spread of HIV could be reduced substantially if newly infected people promptly learned of their status, reduced high-risk behaviors, and when clinically indicated, began and continued treatment that suppresses viral replication. But few if any jurisdictions even attempt to monitor whether all HIV-infected people receive effective treatment, let alone intervene to provide additional support when patients do not start, discontinue, or do not respond well to treatment. New York City, which has one of the nation’s strongest case-management infrastructures, has no systematic citywide information available on whether patients have begun, are continuing, or have a virologic response to treatment.

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**Conclusions**

Proven interventions, such as the use of condoms, clean needles, and expanded voluntary screening, and linkage to care, could prevent most HIV infections. Improving community-based efforts and counseling of individual patients to prevent transmission, supporting patients to facilitate their return to care, and improving the availability of effective treatment could further reduce transmission. But 25 years into the epidemic, we do not consistently apply these proven strategies.

Cost-effective programs include mass-media education campaigns, efforts to make condoms widely available, and interventions to change high-risk behavior in groups with a high prevalence of HIV infection. Routine, voluntary screening for HIV is indicated on the basis of clinical efficacy and cost-effectiveness, and the cost is moderate, as compared with that of many other health interventions. Notification of an infected person’s partners after counseling and testing prevents infections and probably saves money.

Using the current CDC estimate of 40,000 new HIV infections per year, the potential to prevent half to two thirds of these infections, and the current average lifetime cost of care for a patient with HIV infection of $200,000, more effective epidemic control would save between $4 billion and $5.4 billion per year. Widespread availability of condoms, syringe-exchange programs, public health notification of the partners of infected persons, and improvement of case management and monitoring systems would be unlikely to cost more than an additional $1 billion to $2 billion per year nationally — two to three times the current CDC funding for HIV prevention.

Controlling epidemics is a fundamental responsibility of the government, working in concert with physicians, patients, and communities. There is a delicate balance between protecting the public and the individual right to privacy. Until we implement prevention programs with proven efficacy more widely, make voluntary screening and linkage to care a normal part of medical care
and expand screening in community settings, and improve treatment, risk reduction, monitoring, and partner notification, we will continue to miss opportunities to reduce the spread of HIV infection.

Some religious and political groups oppose the use of effective prevention measures. Some advocacy groups oppose expansion of screening and funding of government programs for prevention and control of HIV infection. Some doctors, health care facilities, and organizations will oppose increased monitoring of treatment efficacy; moreover, this cannot be accomplished without additional resources. There are few models for this approach, although Malawi has begun to apply public health principles to testing, treatment, and monitoring.25 Although stigma and discrimination on the basis of sexual orientation continue, advocacy has resulted in substantial progress, including antidiscrimination statutes in many states and increasing numbers of jurisdictions that recognize the rights of domestic partners. The world has changed in the past 25 years, and approaches to HIV prevention must also change. If we fully apply public health principles to the HIV epidemic, we can improve the health of people living with HIV infection and prevent tens of thousands of people in this country from becoming infected with HIV in the next decade.

We are indebted to Drew Blakeman for assistance in the preparation of the manuscript and to Colin McCord and Mark Barnes for helpful comments.

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Medical vs. Surgical Management of Early Pregnancy Failure

TO THE EDITOR: The article by Zhang et al. (Aug. 25 issue) demonstrated the usefulness of treatment of early pregnancy failure with intravaginal misoprostol but did not describe the serious complications that can arise from such administration of this drug. Although endometritis requiring hospitalization was rare in the study by Zhang et al., the Centers for Disease Control and Prevention and Fischer et al. (in this issue of the Journal) have reported that five women died of toxic shock after endometrial infection with Clostridium sordellii in the United States and Canada after medical abortions with mifepristone and intravaginal misoprostol.

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TO THE EDITOR: Zhang et al. report that the rate of complete abortion in the misoprostol group was only 84 percent. We are concerned that the criteria used to diagnose a complete abortion were too stringent and wonder if patients who actually had a complete abortion were misclassified as having had an incomplete abortion.

Sadan et al. found that the false positive rate is 28.9 percent for ultrasonography in predicting retained products of conception after abortion when an endometrial thickness greater than 8 mm is used as the criterion, which is a lower cutoff than the 30 mm cited by Zhang et al. The study by Zhang et al. did not include the pathological results for the women who underwent a surgical evacuation for presumed retained products of conception after initial treatment with misoprostol. We wonder what proportion of the women who were classified as having had an incomplete abortion had negative pathological results after surgical evacuation, which would suggest a completed medical procedure. If these women were given more time, we suggest that the findings on ultrasonography would have normalized without intervention, possibly leading to a higher success rate for the medical regimen.

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THE AUTHORS REPLY: As noted by Shukunami et al., five cases of maternal death due to toxic shock syndrome associated with *C. sordellii* infection have been reported after medical abortion in the United States and Canada since 2001. Clostridium species are part of normal vaginal flora and are found in the vagina of 4 to 18 percent of normal, healthy, nonpregnant women, though *C. sordellii* is a nondominant species. To date, it is unclear if these infections were related to the ascension of resident flora, to mifepristone, or to the vaginal administration of misoprostol. Thousands of women use intravaginal misoprostol for the induction of labor and medical abortion each year. Fatal *C. sordellii* toxic shock syndrome in such cases is extremely rare, which, in our view, is the best evidence for the safety of vaginal misoprostol. It is further noteworthy that the cited cases of medical abortion used both mifepristone (a progesterone and glucocorticoid antagonist) and misoprostol (a prostaglandin E1 analogue), whereas our regimen used misoprostol alone. We agree with the Food and Drug Administration advisory that physicians need to be aware of the possibility of toxic shock syndrome associated with *C. sordellii* infection. Prophylactic antibiotic use is not necessary for this indication and may even be counterproductive.

In the study by Sadan et al. cited by Grotegut and Dandolu, 29 percent of women with an endometrial thickness greater than 8 mm after first-trimester spontaneous or induced abortion did not have retained products of conception. It is tenuous to assume that the false positive rate would remain the same for women with an endometrial thickness greater than 30 mm in our study. In fact, none of the 76 vacuum-aspiration procedures performed in the women treated with misoprostol were for the indication of an endometrial thickness exceeding 30 mm. Therefore, the success rate in our study was not affected by our criterion for endometrial thickness. We agree that endometrial thickness alone may not be a sensitive indicator of the need for vacuum aspiration, as demonstrated in our previous study. For the purpose of research, however, we had to set a cutoff point to standardize care within the study, thus permitting an objective estimate of efficacy.

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Drug-Eluting Coronary Stents

TO THE EDITOR: The article by Dibra et al. (Aug. 18 issue) advances our understanding of the differences between paclitaxel-eluting stents and sirolimus-eluting stents when used to prevent restenosis in patients with diabetes. However, in this study, the rate of in-segment restenosis was 16.5 percent in the paclitaxel-stent group and only 6.9 percent in the sirolimus-stent group (P=0.03) at nine months after intervention, and revascularization was performed in lesions that were complex (type B2 or C) in a high percentage; 74 percent in the paclitaxel-stent group, and 82 percent in the sirolimus-stent group. This is very different from the results of other studies in patients with diabetes, such as the SIRIUS (Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary-Artery Lesions) trial, in which the rate of in-segment restenosis in the sirolimus-stent group was higher than that in the sirolimus-stent group in the study by Dibra et al. (18 percent vs. 6.9 percent at nine months) despite fewer complex lesions (59 percent vs. 82 percent) and without the inclusion of a target lesion in an ostium, a bifurcation, or an...
“unprotected” left main coronary artery or treatment of nontarget lesions in the same or a different coronary vessel during the index procedure. Do the authors have an explanation for this difference?

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TO THE EDITOR: Dibra et al. reported more effective prevention of restenosis with the use of sirolimus-eluting stents than with paclitaxel-eluting stents in patients with diabetes. However, their findings may have resulted from factors not related to the antiproliferative agents used in the stents studied. Selective angiotensin II type 1–receptor blockers (ARBs) have been shown to prevent restenosis after stent implantation1; statins — used alone or in combination with ARBs — exert a similar effect.2 Surprisingly, the authors did not provide any data, particularly at the end of the follow-up period, regarding the use of these drugs, although 70 to 80 percent of the patients presented with hypertension, hypercholesterolemia, or both. Moreover, since diabetes is a progressive disease, blood glucose control and diabetes treatment may have changed during follow-up and thus influenced the course of coronary atherosclerosis,3 but again no data were given. Because glycemic control and vascular drugs affect endothelial function and structure, excluding these potential confounding factors raises doubts about the investigators’ conclusion that sirolimus-eluting stents are superior in patients with diabetes.

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TO THE EDITOR: Windecker et al. (Aug. 18 issue)1 reported the results of a randomized clinical trial called SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization). Despite a late luminal loss within the stent of about 0.3 mm in the paclitaxel-stent group, similar to that observed in the TAXUS-IV trial,2 the incidence of target-lesion revascularization was significantly higher in the trial by Windecker et al. (8.3 percent, vs. 3.0 percent in the TAXUS-IV trial). We are wondering whether this difference may be attributed to very liberal performance of target-lesion revascularization in the SIRTAX trial, possibly as a result of different protocol requirements.

In cases of angiographically moderate restenosis, proven ischemia was required by the TAXUS-IV protocol to proceed to target-lesion revascularization, whereas symptoms were considered sufficient reason in the study by Windecker et al.1,2 Therefore, it would be helpful if Windecker et al. could provide details concerning the rate of target-lesion revascularization performed in patients who, at entry into the study, gave consent for follow-up angiography as compared with the rate in those who gave consent for only clinical follow-up.

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TO THE EDITOR: The comparative trials of sirolimus-eluting and paclitaxel-eluting stents, accompanied by an editorial,1 led to the conclusion that sirolimus-eluting stents “provide an angiographic and clinical edge” over paclitaxel-eluting stents. This assumption, driven by single-center
trials with nonblinded randomization, may be incorrect and misleading. It contradicts the results of the REALITY (Prospective Randomized Multicenter Head-to-Head Comparison of the Sirolimus-Eluting Stent [Cypher] and the Paclitaxel-Eluting Stent [Taxus]) trial, which failed to detect differences in restenosis or any clinical events and in whose group with diabetes paclitaxel was favored with respect to in-lesion restenosis.

In the SIRIAX trial, baseline characteristics of the patients were similar to those of patients enrolled in the SIRIUS and the TAXUS-IV trials. Although the results in the sirolimus-stent group in the SIRIAX trial are similar to those in the SIRIUS trial, the restenosis and revascularization rates in the paclitaxel-stent group of the SIRIAX trial are higher than those in the TAXUS-IV trial. It is hard to imagine that the biology is changing across continents. We believe that the conclusion of stent superiority should be driven only by trials that are blinded, randomized, and adequately powered (>80 percent) with clinically relevant end points in order to avert unnecessary confusion for patients and cardiologists.

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TO THE EDITOR: After reviewing the results of the SIRIAX trial, by Windecker et al., and the Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents (ISAR-DIABETES) trial, by Dibra et al., we disagree with the comment of Moliterno, the editorialist, that sirolimus stents “provide an angiographic and clinical edge over . . . paclitaxel-eluting stents.” A 44 percent reduction in the relative risk of target-lesion revascularization is not merely an “edge,” particularly given the high event rate in question (1.2 million coronary interventions annually).

Moliterno also states that the benefits were driven by soft outcomes, although coronary interventions are usually undertaken to improve angina and the quality of life. It would be unreasonable to expect differences in hard outcomes without much larger or longer trials. We also disagree that a “paclitaxel-eluting stent holds an edge on . . . deliverability . . . ,” since successful implantation was achieved equally (99 percent) with both stents. Although it is true that the differences in outcome may be attributed to any of the three components of the drug-eluting stents, it is fair to conclude that the currently available sirolimus stents do not simply provide a clinical edge over their paclitaxel counterparts but, rather, represent a superior treatment strategy.

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Dr. Jneid reports having received a research grant and consulting fees from Boston Scientific and honoraria from Cordis and Johnson & Johnson.


DR. DIBRA AND COLLEAGUES REPLY: Dr. Alarcón and colleagues point out the difference in angiographic-restenosis rates between patients in the sirolimus-stent group of our study and the subgroup of patients with diabetes in the sirolimus-stent group in the SIRIUS trial. However, results of subgroup analyses are not always reliable. Indeed, subgroup analyses of diabetic patients treated with sirolimus-eluting stents showed a restenosis rate of 17.6 percent in the SIRIUS trial and no restenosis at all in the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) trial. Only two randomized studies have specifically evaluated the use of sirolimus-eluting stents in diabetic patients; the restenosis rates were 7.7 percent in the DIABETES (Diabetes and Sirolimus-Eluting Stent) study and 6.9 percent in our ISAR-DIABETES study.

Dr. Czupryniak and colleagues are concerned about a potential bias introduced in the resteno-
sis analysis by possible differences in glycemic control and in the use of selective ARBs and statins between the two groups in our study. Although there is insufficient evidence to support an influence of these factors on restenosis, we expanded our analysis to address these issues. There were no significant differences in either glycemic control or concomitant therapy between the two study groups. At the time of follow-up angiography, the mean (±SD) level of glycosylated hemoglobin was 7.3±1.1 percent among patients in the paclitaxel-stent group and 7.1±1.1 percent among patients in the sirolimus-stent group (P = 0.28). After discharge, 5.6 percent of the patients in the paclitaxel-stent group and 4.0 percent in the sirolimus-stent group received ARBs (P = 0.72); 85.6 percent of the patients in the paclitaxel-stent group and 84.8 percent in the sirolimus-stent group received statins (P = 0.86); 88.8 percent of the patients in the paclitaxel-stent group and 88.0 percent of the patients in the sirolimus-stent group received angiotensin-converting–enzyme inhibitors (P = 0.84); and 96.8 percent of the patients in the paclitaxel-stent group and 94.4 percent of the patients in the sirolimus-stent group received beta-blockers (P = 0.35). Adnan Kastrati, M.D.
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Since publication of the article, Dr. Kastrati reports having received lecture fees from Bristol-Myers Squibb, Cordis, Lilly, and Medtronic.


DR. WINDECKER AND COLLEAGUES REPLY: Drs. Bonvini and Verin correctly outline differences in the definition of target-lesion revascularization between the SIRTAX and TAXUS-IV trials. However, SIRTAX was a multilesion trial, and therefore the rate of target-lesion revascularization, reported per patient, should be higher than in a single-lesion study such as TAXUS-IV. The rate of target-lesion revascularization per lesion in SIRTAX was 3.5 percent for the sirolimus group and 5.9 percent for the paclitaxel group. The following considerations further substantiate our findings. First, the SIRTAX definition of target-lesion revascularization is common to many coronary-stent trials, including SIRIUS, and reflects clinical practice to intervene in symptomatic patients with stenoses of 50 percent or more. Second, severe late loss (≥1.2 mm) occurred more frequently with paclitaxel than with sirolimus stents (10.7 percent vs. 5.8 percent, P = 0.02). Third, differences in rates of target-lesion revascularization persisted after a post hoc analysis disregarding revascularization driven exclusively by angiography (4.4 percent in the sirolimus-stent group vs. 7.1 percent in the paclitaxel-stent group, P = 0.07). Fourth, rates of target-vessel failure at six months (4.2 percent in the sirolimus-stent group vs. 7.1 percent in the paclitaxel-stent group, P = 0.05) were different before follow-up angiography and similar to those in BASKET (Basel Stent Cost-Effectiveness Trial), another trial comparing sirolimus and paclitaxel stents in a real-world setting (5.7 percent vs. 8.5 percent, P not significant). Fifth, a meta-analysis of six randomized trials comparing sirolimus and paclitaxel stents showed rates of target-lesion revascularization (5.1 percent in the sirolimus-stent group vs. 7.8 percent in the paclitaxel-stent group, P = 0.001) that were similar to those in SIRTAX.

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DR. MOLITERNO REPLIES: The sharply contrasting views of respected leaders, as illustrated by the letters of Drs. Waksman and Wolfram and Dr. Jneid et al., demonstrate the need for large-scale trials...
in the era of drug-eluting stents. My interpretation of SIRTAX and ISAR-DIABETES is supported by a separate meta-analysis.1 This study included all randomized head-to-head trials of drug-eluting stents and 3669 patients (5 percent from a single-center trial, 58 percent from two-center trials, and 37 percent from a multicenter trial). The odds ratio for target-vessel revascularization was 0.64 (95 percent confidence interval, 0.49 to 0.84) favoring the sirolimus-eluting stent. Although the largest study, REALITY,2 found no difference between the stents, it did have low rates of late luminal loss and revascularization. The odds ratio for target-vessel revascularization in the REALITY trial was 0.92 (95 percent confidence interval, 0.57 to 1.49), favoring the sirolimus-eluting stent, and fits within the confidence intervals of all the previous trials, suggesting that it is in fact consistent with them.

With respect to the comments of Jneid et al.: the overall odds ratio for target-vessel revascularization of 0.64 translates into a 34 percent reduction in risk with sirolimus-eluting stents, which is comparable to the reduction in restenosis provided by bare-metal stents as compared with balloon angioplasty. As noted by Drs. Waksman and Wolfram, the data driving this difference in target-vessel revascularization are from a limited number of study centers. So, if we choose to look most skeptically at these results and consider only the upper confidence limit, the relative risk reduction could be as low as 14 percent and the absolute risk reduction would be as low as 1.1 percent. This weakest-effect scenario means that approximately 90 patients would need to be treated with a sirolimus-eluting stent, rather than a paclitaxel-eluting stent, to prevent one additional target-vessel revascularization. Yet, among patient groups with higher rates of average late luminal loss and clinical restenosis, the benefit of sirolimus-eluting stents appears more distinct.

Jneid et al. disagree with my notion that the Taxus stent has an edge in deliverability. Admittedly, I based this view on my personal experience and that of many colleagues. I do not agree that the similar rates of successful stent implantation from a selected cohort indicate similar deliverability. We would have to presume that the guide support, wire stiffness, extent of predilation, and procedural fluoroscopic times were the same in order for these two stents to be deemed similar in this regard.

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TO THE EDITOR: In the article by Pinto et al. (Sept. 1 issue),4 the examination of the sailor presenting with dyspnea and weight gain revealed that his “jugular venous pressure was not elevated,” leading the discussant to dismiss a cardiac cause. In fact, the jugular venous pressure should have been elevated in this patient, who had a pericardial effusion severe enough to cause peripheral edema, ascites, pleural effusions, and hepatic congestion with transaminitis and coagulopathy.

When reclining patients are examined, a markedly elevated jugular venous pressure can be misinterpreted as “not elevated” because of obstruction by the ear or jaw. Borst and Molhuysen described the proper technique for measuring jugular venous pressure as follows:5 “The position of the patient must be adapted so that the pulsations are visible preferably midway between the clavicle and the jaw. Patients with normal or low central venous pressure have to be positioned horizontally.”

This case highlights the importance of reporting the exact measurement of jugular venous pressure, rather than simply stating whether it is elevated.3 We wonder whether the inferior vena cava was dilated on the initial echocardiogram, since...
this would favor an elevated jugular venous pressure that perhaps was not recognized owing to improper positioning of the patient.

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THE AUTHORS REPLY: We agree with Drs. Daniels and Krummen that, barring a process such as hepatic-vein thrombosis with an incidental, hemodynamically insignificant pericardial effusion, elevation of jugular venous pressure should have been detected. Considerable variation exists in expertise in the measurement of jugular venous pressure, and studies indicate poor reliability of such assessments in critically ill patients. This patient subsequently was found to have plethora of the inferior vena cava on echocardiography, reflecting elevated right atrial pressure and signifying that the initial interpretation of the jugular venous pressure was probably incorrect.

Though one may be tempted to ensure complete agreement of all historical and physical findings with the patient’s subsequent diagnosis, we chose to present details as they unfolded and as they were documented by the clinicians. We recognize that clinicians often consider broad differential diagnoses and commonly are faced with incongruent elements of a case. Consequently, one challenge is the integration of data and the determination of whether to discount or question inconsistencies. We hope that presenting the case in this manner accurately portrays the complex decision making that is necessary in routine practice, especially when conflicting or imprecise information exists.

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Medical Mystery: Brown Eye and Blue Eye — The Answer

TO THE EDITOR: The Medical Mystery in the October 6 issue1 shows a 10-year-old boy with one brown and one blue eye, with mild ptosis and miosis of the lighter, left eye (Fig. 1). Both eyes respond equally to light and have normal vision; both are normal on funduscopic examination. The eyes of the boy’s father are blue, and the mother’s are gray. At 10 months of age, the boy was given a diagnosis of a left-sided paraspinal neuroblastoma (C7), extending to the upper thoracic vertebrae and entering the intraspinal canal, with bone marrow involvement (stage 4). After undergoing emergency decompression, chemotherapy, and surgery, the boy is in complete remission but has a loss of sweating (anhidrosis) on the left side of the face and torso. This finding is compatible with left Horner’s syndrome, a regional disturbance of the sympathetic nervous system caused by the paravertebral tumor. A unilateral lack of sympathetic stimulation in childhood interferes with melanin pigmentation of the melanocytes in the superficial stroma of the iris, re-

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Figure 1. One Brown Eye and One Blue Eye.
sulting in heterochromia. This clinical finding might be useful in the early diagnosis of lesions affecting the sympathetic nerves.

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Editor's note: We received 1642 responses to this medical mystery, including 54 percent from physicians in practice, 19 percent from physicians in training, and 14 percent from medical students.

Responses were received from 77 countries. Of the respondents, 71 percent correctly identified Horner’s syndrome (which is sometimes called the Horner–Bernard syndrome) with heterochromia; 21 percent correctly identified the lesion as a cervical neuroblastoma impinging on the sympathetic chain. Other respondents provided such answers as Waardenburg’s syndrome, retinoblastoma, chimerism, Fuchs’ syndrome, and varicella. In addition to the classic findings of Horner’s syndrome and heterochromia, this case highlights the importance of sympathetic innervation for proper melanocyte activity in the iris. Pigmentation of the iris is usually complete by the age of two years.

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Domino Hepatic Transplantation in Maple Syrup Urine Disease

TO THE EDITOR: Orthotopic liver transplantation has been performed in at least 10 patients who have maple syrup urine disease (MSUD)1–4. In the first patients, transplantation was for nonmetabolic reasons (hepatic failure with hepatitis A3 and hypervitaminosis A4). In all patients, there was marked improvement in dietary protein tolerance and no evidence of any decompensation episodes during follow-up extending 10 years.3 Because the long-term outcome and effect on neurologic development remain to be identified, orthotopic liver transplantation remains a controversial therapy.1 With recent reports of success, it has been established as an option for patients with MSUD whose condition fails to respond to medical management.

Many patients with approved indications for orthotopic liver transplantation die before grafts become available (in 2004, approximately 18,000 patients were on the waiting list for transplants, 6168 of whom received them).

We performed an orthotopic liver transplantation in a 25-year-old man (Patient 1) with MSUD and frequent episodes of decompensation, including six hospitalizations over 18 months for ataxia and plasma levels of leucine higher than 1000 µmol per liter (13 mg per deciliter). We used his liver as a domino graft (the use of an explanted liver from a patient with a metabolic disease as a graft in another patient in need of a transplant) in a 53-year-old man (Patient 2) with hepatitis C and hepatocellular carcinoma, who had low priority on the transplant waiting list and was unlikely to survive until routine procurement. Both transplantations were performed “piggyback,” with the domino graft reconstructed with caval segments from a cadaveric donor; accordingly, neither patient required venovenous bypass. Plasma levels of amino acids (Table 1) and apparent whole-body leucine oxidation levels5 (low levels indicating MSUD) were measured before and after transplan-

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Table 1. Plasma Levels of Amino Acids before and after Liver Transplantation.6

<table>
<thead>
<tr>
<th>Patient</th>
<th>Leucine</th>
<th>Isoleucine</th>
<th>Valine</th>
<th>Alloisoleucine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before transplantation</td>
<td>544±234</td>
<td>240±135</td>
<td>286±118</td>
<td>250±67</td>
</tr>
<tr>
<td>After transplantation</td>
<td>203±36</td>
<td>110±25</td>
<td>280±54</td>
<td>16±7</td>
</tr>
<tr>
<td><strong>Patient 2‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before transplantation</td>
<td>183±15</td>
<td>90±9</td>
<td>286±21</td>
<td>0</td>
</tr>
<tr>
<td>After transplantation</td>
<td>179±37</td>
<td>93±23</td>
<td>270±50</td>
<td>0</td>
</tr>
<tr>
<td><strong>Patient 3§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before transplantation</td>
<td>092</td>
<td>38</td>
<td>141</td>
<td>0</td>
</tr>
<tr>
<td>After transplantation</td>
<td>112</td>
<td>34</td>
<td>146</td>
<td>0</td>
</tr>
<tr>
<td>Normal range</td>
<td>75–175</td>
<td>36–98</td>
<td>141–317</td>
<td>0</td>
</tr>
</tbody>
</table>

† Patient 1 had maple syrup urine disease. Patient 2 had hepatitis C and hepatocellular carcinoma and received a liver graft from Patient 1. Patient 3 was a control who had hepatitis C and hepatocellular carcinoma and received a liver transplant from a cadaveric donor. Plus–minus values are means ±SD.
‡ For Patient 2, amino acid levels were measured in 2 samples before transplantation and 26 samples after transplantation.
§ For Patient 3, amino acid levels were measured in one sample before and after transplantation.
tation in both patients and in a control (Patient 3), a 47-year-old woman who had hepatitis C and hepatocellular carcinoma but who was eligible for transplantation through the usual channels. Surgical outcomes were good. Patient 1 had marked decreases in plasma levels of branched-chain amino acids and alloisoleucine (Table 1), despite increased dietary protein from 6 g to more than 40 g per day. Patient 2 maintained near-normal amino acid levels with no detectable alloisoleucine on an unrestricted diet, reflecting the role of extrahepatic metabolism of branched-chain amino acids. Leucine oxidation (unchanged in Patient 3) increased in Patient 1 and decreased in Patient 2; after transplantation, both patients had levels of whole-body leucine oxidation expected in patients with heterozygosity for MSUD. Both patients have tolerated normal protein intake without any symptoms of MSUD for more than 12 months.

We conclude that liver transplantation substantially corrects whole-body branched-chain amino acid metabolism in patients with MSUD and greatly attenuates the disease. Livers from patients with MSUD may be considered as domino grafts for patients who have low priority on the transplant waiting list and who are likely to die without a transplant.

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John Hunter is rightly regarded as the founder of scientific surgery, but he has long been a lightning rod for controversy, within his own lifetime and even today. In this new biography, Wendy Moore brings Hunter to life in all his flawed, combustible glory.

As a young man, Hunter left the hardscrabble Scottish Lowlands to join his doctor brother William in 18th-century London, eventually becoming the most famous physician in England. Hunter, blessed and cursed by an insatiable natural curiosity, made enormous contributions to anatomy and embryology. (These achievements were made possible by the thousands of cadavers pilfered for Hunter by the professional grave robbers known as resurrection men.) He pioneered limb-saving treatment for popliteal aneurysm, an occupational illness of coachmen caused by repetitive trauma from their high-top leather boots as their carriages bounced over the cobblestones. Hunter also experimented with artificial insemination, tooth transplantation, collateral circulation, and bone growth and remodeling. In addition, he was a naturalist who anticipated much of Darwin’s theory of evolution.

Hunter was no bookman. He disdained scholarly study, particularly the prevailing orthodoxies of Galen, in favor of personal observation and investigation. As Hunter once wrote to his favorite student, Edward Jenner, “I think your solution is just, but why think? Why not try the experiment?” Hunter concluded from clinical experience, including his early placebo studies, that the contemporary cure-alls of bleeding, purging, and mercury were useless. These views were so radical at the time that 50 years after his death the editors of Hunter’s collected works were still apologizing for them. Hunter was also keenly aware of the current limitations of surgery — he likened a surgeon to “an armed savage who attempts to get that by force which a civilized man would get by stratagem.”

On occasion, Hunter’s zeal for experimentation misfired. In a disastrous attempt to determine whether syphilis and gonorrhea were distinct conditions, he inoculated gonorrheal pus from a patient into the genitals of an uninfected subject. Unfortunately, Hunter’s source patient was infected with both gonorrhea and syphilis. When the subject developed symptoms of both, Hunter wrongly concluded that the two diseases were different aspects of the same illness. Moore agrees with the conclusions of most scholars that this was self-experimentation, citing the assertions of Hunter’s editors and students’ transcripts of Hunter’s lectures, in which he referred to himself as the unlucky subject.

In some respects, Hunter resembled Surgeon Cuticle in Herman Melville’s White Jacket, whose “long habituation to the dissecting-room and amputation-table had made him seemingly im-
pervious to the ordinary emotions of humanity.” Hunter’s obsessive collecting sometimes led him to transgress the bounds of common decency. As the Irish giant Charles Byrne was dying of tuberculosis, Hunter became obsessed with obtaining his corpse, hiring henchmen to follow the giant around London. The horrified Byrne then arranged for his body to be sunk in the Irish Sea on his death. Hunter spent a fortune bribing the undertaker, who switched the giant’s body for paving stones at a tavern on the route to the coast, while Byrne’s inebriated burial party slumbered. Hunter’s ruthlessness in the service of science captured the public imagination and may have influenced early literary depictions of the mad scientist. Notably, Robert Louis Stevenson used Hunter’s London residence as the sinister setting for *The Strange Case of Dr. Jekyll and Mr. Hyde* (1886).

Hunter’s iconoclasm made him beloved by his pupils and despised by his peers. Wealth and notoriety did nothing to improve his temperament, and he became more cantankerous with age. After Hunter dropped dead of angina during a particularly acrimonious staff meeting, one of the first acts of his surviving hospital colleagues was to sponsor the writing of a defamatory biography. Moore provides a largely sympathetic assessment of Hunter’s ambiguous legacy. Her complex portrayal nicely balances the rigor of the historian with the art of the storyteller. *The Knife Man* makes for fascinating, often macabre reading, and it will be enjoyed by anyone with an interest in the history of medicine.

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**INTERFERON: THE SCIENCE AND SELLING OF A MIRACLE DRUG**


In 1957, the discovery of an antiviral agent that could rival the bactericidal power of penicillin generated excitement in government, industry, the media, and the general public. Nearly 50 years later, this class of biologic agents collectively called interferons generates a $5 billion global drug market.

In *Interferon: The Science and Selling of a Miracle Drug*, Toine Pieters charts the culture of medical research in the mid-to-late 20th century, the blossoming of biotechnology, the politics of scientific research, the influence of the media, and the pressure of lobbies for patients.

What is particularly effective (and accurate) in Pieters’s book is the detailed story of the early years of interferon research — a story of a dedicated band of believers who kept faith in the face of conflicting data and impure preparations of variable potency. Pieters captures the pioneering atmosphere of those days very well. In this era of biologicals — when hundreds of molecularly defined, pure recombinant cytokines can be ordered for next-day delivery — it is easy to forget that at one time the best interferon source in the world had only 0.1 percent purity and was made from Sendai virus–stimulated human leukocytes. For many years, scientists doubted the very existence of interferon and its antiviral activity. Indeed, as late as 1977, when I started a postdoctoral fellowship with the interferon researcher Joyce Taylor, the immunologist Peter Alexander said to me, “But Fran, you cannot work with interferon — it doesn’t exist!” Just three years later, the first (of many) human interferon genes was cloned by Biogen and Schering-Plough.

The interferons (there are 4 main types and more than 20 subtypes with the shared ability to induce an antiviral state in cells) blazed the biotechnology trail. Their story illustrates the challenge of developing therapeutic proteins. Interferon research also laid the foundation of cytokine biology, defining the unexpected hallmarks of this important group of intercellular communicators: families of proteins with pleiotropic effects on homeostasis and disease, species specificity, byzantine regulatory mechanisms, activity in picomolar or femtomolar amounts, and key roles in both innate and adaptive immunity.

In the 1970s, interferon was a magic bullet, a wonder drug that could cure all ills, especially cancer. Pieters writes, “The picture conveyed . . . interferon as a somewhat mysterious, clinically unharnessed, non-toxic natural body substance that was claimed to be the hottest, though long ignored, line of medical research currently being followed.” The media gave the impression that if only there were enough of this extremely scarce and expensive natural protein, everything from chickenpox to cancer would be cured. Virologist Mathilde Krim and oncologist
Jordan Gutterman lobbied Congress so effectively that 3 percent of the annual National Cancer Institute budget was earmarked for the Biological Response Modifier Program on the condition that the focus would be on interferon. The interferon message was one of promise and hope, and the media coverage in the 1970s and 1980s mirrored the expectations and opinions of those in the biomedical realm.

The history of interferon, which must be considered to be recent, is full of surprises. For instance, in 2005, when it takes months and mountains of paper before permission is granted by an ethics review board to conduct the simplest clinical trial, it seems amazing that the first clinical studies with interferon alpha used historical controls and very small numbers of patients. But this protocol was not particularly unusual for that time. We learn in Pieters’s book that in the 1970s, many oncologists claimed that randomization in clinical trials was neither ethical nor necessary.

When there was enough interferon to go around for properly conducted clinical trials, however, the results were disappointing and the interferons were consigned for many years to the status of orphan drugs for rare terminal diseases. Their slow and continuing transformation into approved and effective drugs for more than 10 diseases is another interesting story but one that is not covered in detail in this book. I found this omission disappointing. However, Pieters focuses on answering one intriguing question: Why does interferon enjoy a public reputation similar to penicillin’s even though it remains a treatment confined almost entirely to specialty diseases? In its answer, the book succeeds admirably.

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PENTOTHAL POSTCARDS

In the current era of e-mailed electronic snapshots, frequent intercontinental travel, and advanced pharmaceutical marketing, picture postcards from abroad bearing promotional messages for drugs might appear quaint or hokey or downright bizarre. Yet in the 1950s and 1960s, drug manufacturer Abbott Laboratories sent physicians and nurse anesthetists about 170 different postcards touting the anesthetic sodium pentothal (thiopental sodium). These postcards, now collector’s items, form the basis of this enjoyable small book by anesthesiologist David C. Lai.

Copies of nearly 90 postcards, showing scenes from some 60 countries, constitute the core of the book. The messages on the postcards appear in varied handwriting, typing, and typesetting, and the cards carry stamps of their lands of origin. Repeatedly, the messages, signed “Abbott,” emphasize the widespread use and established record of the product. “In vast and sparsely populated Greenland you’ll find PENTOTHAL in use, as it is wherever modern medicine is practiced,” begins a postcard showing native sealers. “The Taj Mahal is justly