



# This Week in the Journal

August 22, 2002

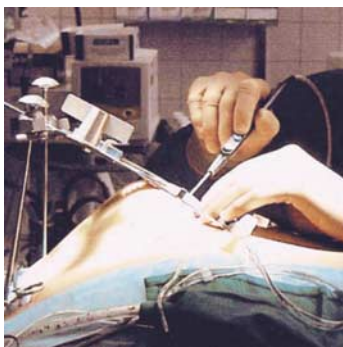


## ***Escherichia coli* O157:H7 Infections among Visitors to a Dairy Farm**

An outbreak of *Escherichia coli* O157:H7 infections was traced to a dairy and petting farm. The 51 patients (median age, four years) included 8 in whom the hemolytic–uremic syndrome developed. Contact with calves was associated with an increased risk of infection. Thirteen percent of the farm’s 216 cattle were colonized with the same strain of *E. coli* that was isolated from the patients.

*This study provides evidence of direct transmission of E. coli O157:H7 from farm animals and their environment to young visitors, especially those who petted the calves. The importance of this mode of transmission may be greater than previously recognized. Careful hand washing after visiting a farm is one strategy to make farms safer for children.*

**see page 555 (editorial, page 608)**

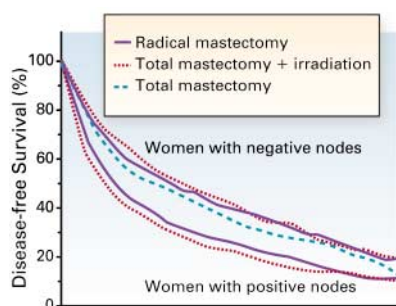


## **Minimally Invasive Coronary-Artery Bypass Surgery**

Minimally invasive bypass surgery and coronary stenting are both alternatives to standard bypass surgery for the management of stenosis of the proximal left anterior descending artery. In this randomized trial, stenting provided excellent short-term results with fewer periprocedural events, but minimally invasive surgery proved better at six months in terms of freedom from angina and the need for repeated procedures.

*Minimally invasive bypass surgery is attractive since it does not require cardiopulmonary bypass, but it is technically challenging because of the limited operative field. Whether it will prove superior to drug-eluting stents, which were not used in this trial, will require additional study.*

**see page 561 (Perspective, page 551)**

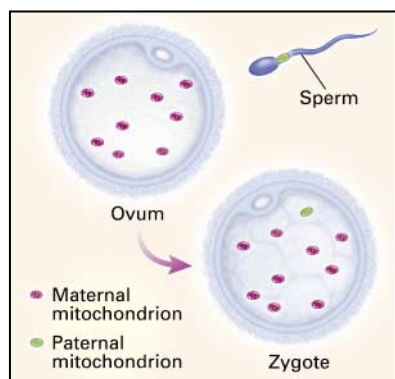


### Radical versus Total Mastectomy

A trial to compare the efficacy of radical mastectomy with that of total mastectomy began in 1971 and enrolled 1665 women with breast cancer. After 10 years of follow-up, radical mastectomy was not superior to total mastectomy. Now, after 25 years of follow-up, 293 of the women are alive and free of breast cancer; radical mastectomy did not show an advantage over total mastectomy.

*This pioneering trial led to a vast improvement in the quality of life for women with breast cancer. It spelled the end of radical mastectomy and started the trend toward less extensive surgery, which culminated in the lumpectomy. Although the treatments used in 1971 for breast cancer are now outmoded, this historic trial set the management of breast cancer on a new course.*

see page 567



### Brief Report: Paternal Mitochondrial DNA

This report describes a 28-year-old man with lifelong exercise intolerance. Evaluation revealed a mitochondrial myopathy due to a novel 2-bp mitochondrial DNA deletion in the *ND2* gene, which codes for a subunit of enzyme complex I of the mitochondrial respiratory chain. Studies of the patient and his immediate family members revealed that the abnormal mitochondrial DNA was paternal in origin and accounted for 90 percent of the mitochondrial DNA in the patient's muscle.

*This finding challenges the assumption that mitochondrial DNA is always maternal in origin.*

see page 576 (editorial, page 609)

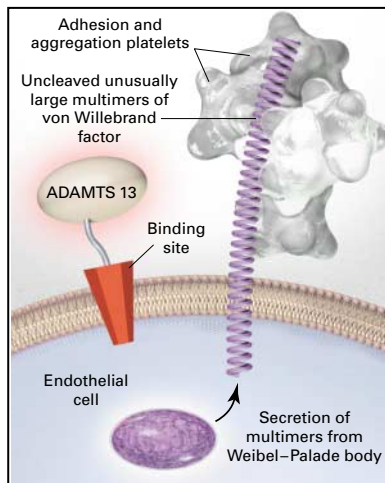
### Special Article: Experiences of Oregon Nurses and Social Workers with Patients Who Requested Assistance with Suicide

*“Patients request assistance with suicide because they want to control the circumstances of death . . . and are ready to die.”*

Physician-assisted suicide was legalized in Oregon with the passage of the Death with Dignity Act in 1997. Seventy-one of the 91 patients who have died by assisted suicide received hospice care. This study reports the results of a survey of hospice nurses and social workers about patients who received prescriptions for lethal medications. Like physicians who responded to a similar survey, hospice nurses and social workers reported that patients chose assisted suicide because they wished to control the circumstances of death, not because they were depressed, lacked social support, or were concerned about being a financial burden. As compared with other hospice patients and their families, patients who received prescriptions for lethal medications appeared to have less pain, depression, and anxiety, and their family caregivers appeared to be less burdened.

*The reports of hospice nurses and social workers in Oregon suggest that the legalization of physician-assisted suicide has not led to its widespread use by the most vulnerable terminally ill patients, such as those who are depressed or socially isolated.*

see page 582



## Mechanisms of Disease: Thrombotic Microangiopathies

This article reviews the substantial progress made in understanding the thrombotic microangiopathies. The mechanisms of both thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome are considered.

*The discovery of the role of unusually large multimers of von Willebrand factor and of the metalloprotease that cleaves these multimers has ignited a new wave of research in thrombotic thrombocytopenic purpura. The mapping of the molecular action of Shiga toxins has illuminated our understanding of the hemolytic–uremic syndrome. These advances are likely to lead to major advances in the treatment of thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome.*

see page 589

## PERSPECTIVE

### Angioplasty versus Minimally Invasive Bypass Surgery

The modern treatment of coronary artery disease began with the development of coronary bypass surgery more than three decades ago, which was followed by the development of coronary angioplasty more than two decades ago. Conventional bypass surgery offers patients excellent long-term revascularization, but it is a highly invasive procedure. By contrast, angioplasty offers minimally invasive revascularization whose effects are tempered by high rates of restenosis. In the past decade, both techniques have evolved, as attempts have been made to decrease the invasiveness of bypass surgery and to decrease the restenosis rate associated with angioplasty.

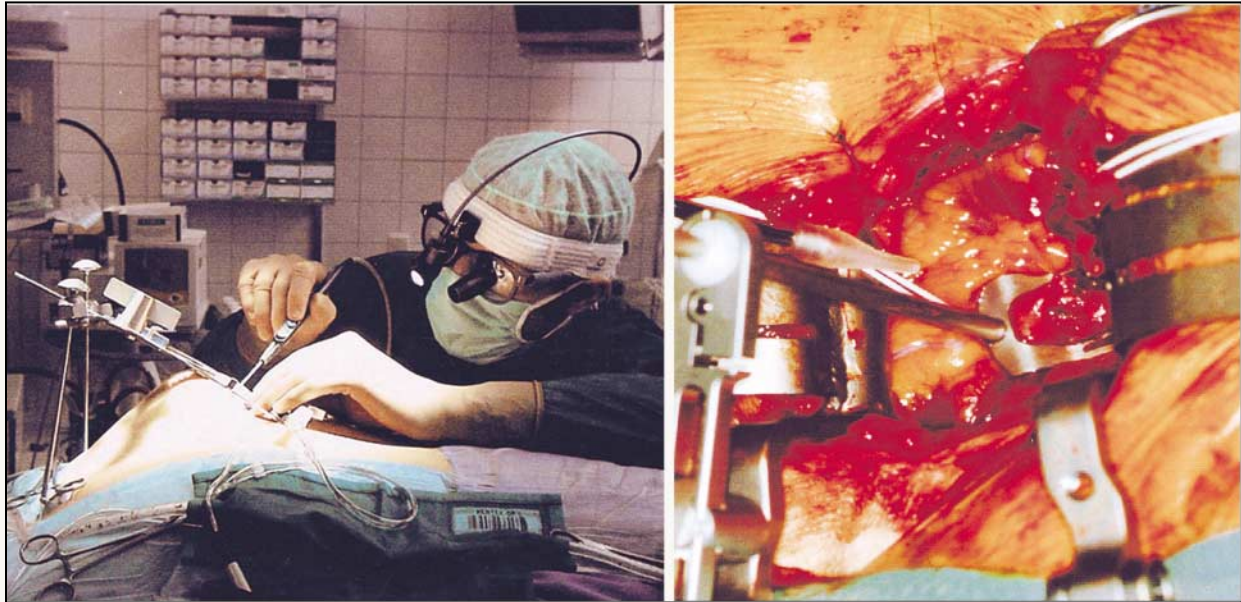
Currently available data, including the results of studies of long-term outcomes with coronary re-

vascularization surgery, are for traditional bypass surgery performed through a sternotomy and using cardiopulmonary bypass and cardioplegia to provide a motionless surgical field. Anatomical issues such as the intramyocardial location or small diameter of coronary arteries do not preclude the use of this surgical approach. The visibility it affords decreases the risk of misidentification of branches of the coronary artery. In modern practice, except for those with major coexisting conditions, the hospital stay for patients undergoing traditional bypass surgery for triple-vessel disease has been reduced to approximately five days, and the hospital stay for single-vessel bypass surgery is now as short as three days. A standard has evolved for a long-term outcome that is considered by many to be a benchmark for analysis of outcomes after treatment of coronary artery disease — traditional bypass surgery in which the left internal thoracic artery is used. Left-internal-thoracic-artery grafts used in the anterior descending coronary artery have patency rates of more than 90 percent at 15 years. Thus, any study comparing long-term outcomes of different treat-

ments for coronary artery disease should also use the outcome standard for traditional coronary artery surgery.

The term “minimally invasive” has been used to describe bypass surgery performed through a smaller incision, bypass surgery performed on the beating heart without the use of cardiopulmonary bypass, or both, as in the report by Diegeler et al. in this issue of the *Journal* (see pages 561–566). Although a shorter incision may be appealing, the benefit is lost if it compromises the revascularization; indeed, studies have suggested that bypass surgery performed through a small incision may be associated with lower patency rates than bypass performed through a sternotomy. Furthermore, the length of the incision does not correlate with the morbidity or mortality associated with the procedure or with the efficacy of the operation.

Because of the potential complications of cardiopulmonary bypass (including neurocognitive impairment), surgeons are evolving techniques to perform bypass surgery — even multiple bypasses — on the beating heart without cardiopulmonary bypass. Avoidance of cardio-



The Surgical Field for Performing Minimally Invasive Coronary Bypass Surgery on the Beating Heart, without the Use of Cardiopulmonary Bypass.

A stabilizing device is used to reduce movement of the arterial segment in which the anastomosis is being constructed.

pulmonary bypass and aortic manipulation (a potential source of embolic debris) may prove to cause fewer complications. Such a procedure can be performed through a sternotomy or through an incision offering minimal access (see Figure). However, randomized, prospective studies have not yet been conducted to determine whether this approach is superior to traditional coronary-artery bypass surgery. A critical test for newer surgical approaches is whether they produce the same long-term patency rates and survival advantage as traditional bypass grafting.

After the introduction of angioplasty, it was recognized that there was a substantial rate of restenosis. Angiopathy also carries risks of complications and death, as Diegeler et al. confirm. Restenosis may occur for a variety of reasons. Some dilated arteries undergo elastic recoil because of fibrosis and calcification of the stenotic arterial segment that cannot be corrected by simple dilation. Dilation with stent implan-

tation has remedied the problem of elastic recoil and reduced the incidence of restenosis. However, restenosis can still occur because of intimal hyperplasia within the stented arterial segment; this may be a particular risk for narrow coronary arteries requiring small-caliber stents. Recent studies using drug-coated stents suggest that these devices reduce the frequency of this important cause of recurrent stenosis, although long-term data are not yet available.

How should physicians choose between angioplasty with stent implantation and revascularization surgery, and how should they decide which approach to use? In some cases, the decision is made because of anatomical considerations — such as the location and type of lesion or the caliber of the artery — that increase the risks associated with angioplasty or the risk of restenosis. The age of the patient and the presence or absence of coexisting conditions that might decrease life expectancy or increase the risk

associated with surgery should be considered. If surgery is elected, the choice of type of incision and the decision about whether to use or avoid cardiopulmonary bypass should take into account the patient's anatomy, the potential complications of the selected approach, and the potential risk of compromising the long-term patency of the graft. Because new options for and approaches to percutaneous intervention and surgery continue to evolve, both the interventional cardiologist and the cardiac surgeon should participate in the formulation of patients' treatment plans. In doing so, the clinicians involved should consider not only issues related to risks, but also those related to long-term patency and the survival of the patient.

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## Beyond Barcelona — The Global Response to HIV

There is a striking contrast between the countries where people are dying from AIDS and the countries where they are receiving effective therapy. In Western nations, there were 25,000 deaths from AIDS in 2001, and about 500,000 people were using antiretroviral drugs against human immunodeficiency virus (HIV) infection (see Figure). In sub-Saharan Africa, however, there were 2.2 million deaths, and only about 25,000 people were receiving antiretroviral treatment.

If there was a single message from this summer's 14th International AIDS Conference in Barcelona, Spain, it was that this situation must change, and change quickly. "Treatment is technically feasible in every part of the world," Dr. Peter Piot, the executive director of the Joint United Nations Program on HIV/AIDS (UNAIDS), said at the opening ceremony. "I don't know a single place in the world where the real reason AIDS treatment is unavailable is that the health infrastructure has exhausted its capacity to deliver it. It's not knowledge that's the barrier. It's political will."

The emphasis on improved access to antiretroviral drugs throughout the world has been catalyzed by the development of effective medications and by sharp price reductions. It also reflects a growing recognition of global interdependence and the devastating impact of the AIDS pandemic. Of the 40 million adults and children living with HIV infection at the end of 2001, roughly 95 percent were in developing countries (see Table). HIV infection is spreading rapidly in many areas, including parts of China, eastern Europe, and central Asia. There are now seven African countries (Botswana, Lesotho, Namibia,

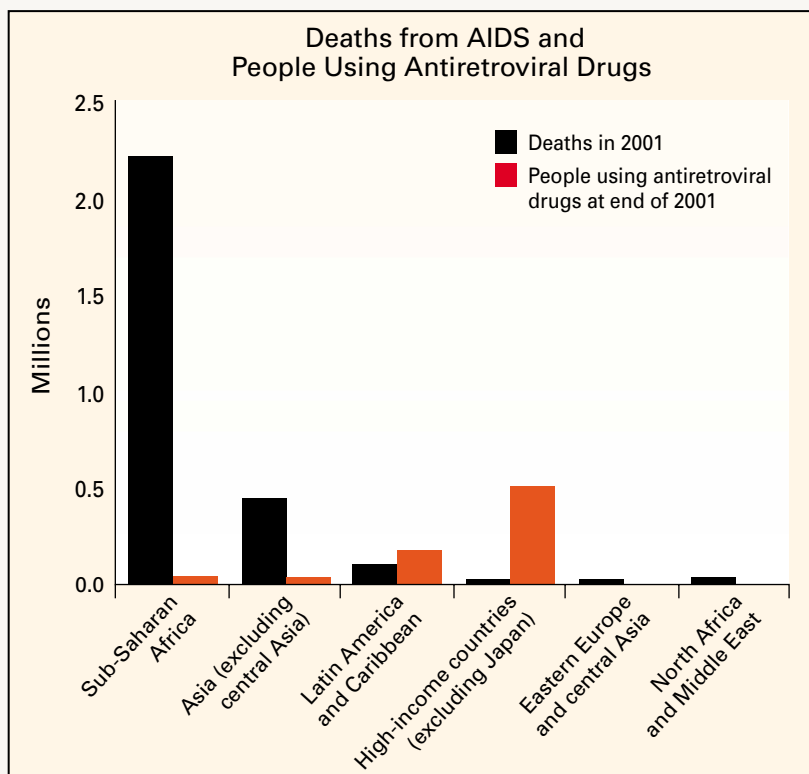


Figure adapted from the UNAIDS Report on the Global HIV/AIDS Epidemic, 2002.

South Africa, Swaziland, Zambia, and Zimbabwe) where more than 1 in 5 people between the ages of 15 and 49 years are infected with HIV, and another six countries where more than 1 in 10 are infected. By 2010, orphans (children under the age of 15 whose mothers, fathers, or both have died) will account for 15 to 25 percent or more of all children in 12 sub-Saharan African countries; most of these children will have lost both their parents to AIDS. Also by 2010, the U.S. Census Bureau projects that life expectancy in some countries in sub-Saharan Africa will fall to near 30 years, levels not seen since the end of the 19th century. Without AIDS, life expectancy in Botswana would be 74 years in 2010; with AIDS it is projected to be 27 years.

The International AIDS Conference is a unique forum that brings together diverse groups, including researchers, practicing physicians, government officials, activists, and

the news media. While researchers presented their findings, Piot and other prominent leaders, such as Nelson Mandela and Bill Clinton, used the conference as a platform from which to galvanize support for more rapid and concerted action. "We cannot lose the war on AIDS and win our battles to reduce poverty, promote stability, advance democracy, and increase peace and prosperity," Clinton said at the closing ceremony.

Ten billion dollars a year is required for a "minimum credible response to the epidemic," according to Piot. The \$10 billion annual figure is more than three times the \$2.8 billion that is currently available from governments, foundations, businesses, and other sources. Another \$3 billion a year is required for treatment and prevention of malaria and tuberculosis.

According to Clinton, "the wealthy nations should determine what each's share of the \$10 billion a year" is and "should pay it." There

The Global HIV–AIDS Epidemic in 2001

Region	People living with HIV–AIDS	Children orphaned by AIDS	Deaths from AIDS
Sub-Saharan Africa	28,500,000	11,000,000	2,200,000
South and Southeast Asia	5,600,000	1,800,000	400,000
Latin America	1,500,000	330,000	60,000
East Asia and Pacific	1,000,000	85,000	35,000
Eastern Europe and central Asia	1,000,000	<5,000	23,000
United States and Canada	950,000	320,000	15,000
Western Europe	550,000	150,000	8,000
North Africa and Middle East	500,000	65,000	30,000
Caribbean	420,000	250,000	40,000
Australia and New Zealand	15,000	<1,000	<100
<b>Estimated global total</b>	<b>40,000,000</b>	<b>14,000,000</b>	<b>3,000,000</b>

Data are from the UNAIDS Report on the Global HIV/AIDS Epidemic, 2002. Children are those under 15 years of age.

are various possible formulas. Under the United Nations system, the United States pays about 22 percent of the costs, followed by Japan, Germany, France, the United Kingdom, and Italy. The \$10 trillion U.S. economy represents about 40 percent of the \$25 trillion economy of the industrialized world. According to the economist Jeffrey D. Sachs, an advisor to United Nations Secretary-General Kofi Annan, the United States should be spending about \$3.5 billion internationally for AIDS, tuberculosis, and malaria in fiscal year 2003. This would represent about a third of the \$10 billion global expenditure for the three diseases that Sachs believes is necessary in the next fiscal year. The total expenditure should increase to \$13 billion or more in the following years. Of the \$3.5 billion from the United States, Sachs recommends that \$2.5 billion go to the Global Fund to Fight AIDS, Tuberculosis, and Malaria and

\$1 billion to bilateral programs. According to figures released at the conference, the Bush administration has requested about \$16 billion for spending on HIV and AIDS in fiscal year 2003 — about \$15 billion for domestic programs and \$1 billion (some for research) for international programs.

For the nations with the world's largest economies, \$10 billion a year is not a lot of money. There is serious concern, however, about whether funds for HIV programs will be spent effectively. The issues include the design of treatment and prevention programs, the cost of antiretroviral drugs, and the likelihood of misuse of funds and diversion of resources. There are inevitable tensions between accountability for the efficient use of resources and unreasonable requirements of proof that programs are changing the course of the epidemic before they can be adequately funded.

The Global Fund to Fight AIDS,

Tuberculosis, and Malaria is an independent, nongovernmental organization based in Geneva that accepts donations from governments and other sources. It should quickly become the largest financing mechanism for HIV programs in the developing world. The next several months are critical. Before the end of October, the Global Fund, in conjunction with the World Health Organization and the United Nations, is expected to finalize its financing plans and make public a plan of action. Governments and private donors will then have to decide whether they accept it and are willing to contribute accordingly. It is not clear that the action plan will become the actual plan.

As the Global Fund commits itself to raising and distributing billions of dollars, the number of people in developing countries who receive antiretroviral therapy should increase substantially. Among the critical needs are outfitting and enlarging both treatment and prevention programs, training physicians and community-based health workers to care for people with HIV infection, and continuing to reduce the prices of effective antiretroviral medications. At the end of 2001, some generic combinations of medications were available for about \$350 per person per year. If the annual cost of antiretroviral therapy could be reduced to no more than \$100 per person per year, treatment would be affordable in many more countries and donations would have a far greater effect.

Millions of people throughout the world are treated each year for tuberculosis, malaria, and other serious infections. By July 2004, when the 15th International AIDS Conference begins in Bangkok, Thailand, it will be clear whether or not millions of people are receiving effective treatments for HIV infection as well.

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