country where the trial is conducted, an international fund, or someone else. Although trial participants are unlikely to need treatment until years after they become infected, they will eventually need it for life.

AIDS prevention and treatment are inextricably linked; it is not possible to deliver one without the other. By August 2008, when the XVII International AIDS Conference is held in Mexico City, it will be clear whether the world is continuing to lose ground to the AIDS pandemic or finally getting ahead of it.

An interview with Mark Wainberg, cochair of the XVI International AIDS Conference, can be heard at www.nejm.org.

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Global Health — The Gates–Buffett Effect

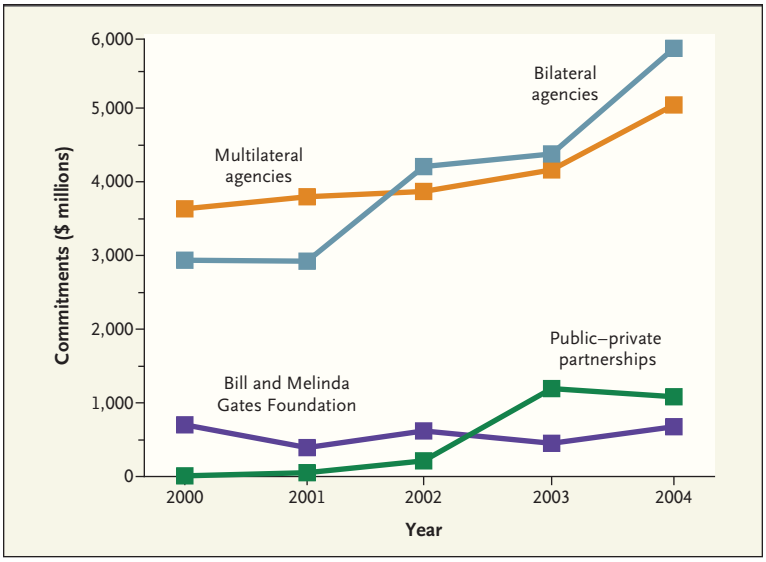
Susan Okie, M.D.

Standing before a giant AIDS ribbon, Bill and Melinda Gates greeted some 26,000 researchers and public health workers on the opening night of last month's conference hosted by the International AIDS Society in Toronto. Bill Gates's voice echoed through the stadium as he assured the conference delegates, "Melinda and I have made stopping AIDS the top priority of our foundation." The Gateses spoke in turn, revealing both their passion and their clear-eyed intellectual engagement. Bill Gates talked of the new optimism he senses in Africa with the increased availability of antiretroviral drugs, but he warned that without increased prevention efforts, the provision of long-term treatment for infected persons is "simply unsustainable." Melinda Gates spoke of the stigmas that limit efforts to control AIDS, noting that government officials in many countries refuse to accompany them when they meet with sex workers. The philanthropists promised to increase their foundation's funding for research on new prevention tools for women and called for expanded access to proven measures such as condoms, clean needles, and HIV testing. The demonstrators who had heckled previous speakers were silent; the Gateses were interrupted only by cheers.

In a world with many celebrities but few heroes, Bill Gates has attained heroic status by committing much of his enormous fortune to the advancement of global equity. He and his wife have targeted the causes of health disparities between rich and poor, and their foundation has become a driving force in international aid and in research on AIDS and other diseases. In June, the Bill and Melinda Gates Foundation's likely impact on global health was amplified when Warren Buffett, the world's second-richest man, announced plans to give most of his fortune to the foundation established by the richest one.

Buffett's gift, worth about $37 billion, will double the foundation's endowment from $29 billion to approximately $60 billion, making it by far the world's largest charitable foundation. The gift will also increase the foundation's annual giving from $1.36 billion last year to about $3 billion, or approximately $1 per year for every person in the poorer half of the world's population. By comparison, the World Bank estimates that total health-related aid to developing countries in 2004 (from governments, international organizations, and private sources) was about $12.7 billion (see graph).

If Gates donates more of his own fortune and if the value of Buffett's donated Berkshire Hathaway stock rises, the Gates Foundation's annual giving will increase further. Yet the projected cost of solving major health problems in the developing world is far higher than even the most optimistic projections for giving by Gates. In 2000, the United Nations adopted Millennium Development Goals to be achieved by 2015; they included substantially reducing child and maternal mortality, reversing the spread of



Development-Assistance Commitments to the Health Sector, 2000 to 2004.

"Bilateral agencies" include those in Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the United Kingdom, and the United States (including the U.S. Agency for International Development). "Multilateral agencies" include United Nations agencies (the World Health Organization, the Joint Programme on HIV–AIDS, the Children's Fund, and the Population Fund), development banks (the World Bank, the Inter-American Development Bank, the Asian Development Bank, the African Development Bank, and the African Development Fund), and the European Union. "Public–private partnerships" include the Global Alliance for Vaccine and Immunization and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Data are from Catherine Michaud of the Harvard Initiative for Global Health, Cambridge, MA.

HIV–AIDS and malaria, and reducing the prevalence of tuberculosis and associated mortality. It is estimated that to meet these health goals, international aid would have to increase by a factor of three to seven.[1]

Shortly after their marriage in 1994, Bill and Melinda Gates designated global health as the primary focus for their charitable giving and established the William H. Gates Foundation. By the end of 2005, the foundation (renamed in 1999) had awarded $10.2 billion in grants, about $6 billion of it for health-related projects. The mission of these grants can be summarized in three words: global health equity. The foundation holds that all human lives are of equal value, and the goal is to conquer diseases that disproportionately afflict the world's poor, preventing them from reaching their full potential. "Until we reduce the burden on the poor so that there is no real gap between us and them," Gates said in 2005, "[global health] will always be our priority."[2]

Some of the earliest major grants of this foundation aimed to increase access to life-saving vaccines in developing countries. Other key targets have included HIV–AIDS, malaria, tuberculosis, malnutrition, acute diarrheal and respiratory infections, tropical parasitic diseases, and maternal and child health. The foundation also mobilizes new resources for global health by promoting innovative financing mechanisms and product development and makes "focused investments . . . to achieve fundamental scientific breakthroughs," as exemplified by $450 million in grants awarded last year to tackle 14 "grand challenges" in infectious disease, nutrition, and other fields. Recently, the foundation has begun to work on development issues that strongly influence health, such as clean water, sanitation, and girls' education.

The foundation has had several notable health-related achievements to date (see box), and some claim that the example set by Bill and Melinda Gates has been as important as the money they've donated. By calling attention to global inequities, they have attracted funding from others and made it fashionable for the rich or famous to become involved in solving global problems. Buffett's move reflects that trend — and seems likely to intensify it. "The golden age of global health started when Bill and Melinda Gates put $27 billion into their foundation," says Jim Yong Kim, chief of the Division of Social Medicine and Health Inequalities at Brigham and Women's Hospital in Boston. "They completely changed the sense of scale. It was the Gateses who really got us dreaming."

"I think people watch what the Gateses do and assume that if they're doing it, it's not only a smart humanitarian move, but a smart business move," said Helene Gayle, a former official at the Centers for Disease Control and Prevention (CDC) who spent 5 years at the Gates Foundation and now heads CARE. "They've put global health on the front burner like never before."

According to Gayle, a trip to

Key Health-Related Achievements of the Gates Foundation

An estimated 1.7 million deaths have been prevented through the work of the Global Alliance for Vaccines and Immunization (GAVI), which was formed in 2000 with the help of Gates funding and has received grants totaling $1.5 billion. About 90 million children have received hepatitis B vaccine, about 14 million have received *Haemophilus influenzae* type B and yellow fever vaccines, and about 21 million have benefited from expanded coverage with basic childhood vaccines. As a partnership of public and private organizations, governments, and pharmaceutical companies, GAVI also represents a successful model for alliances that the Gates Foundation is promoting in other areas.

An HIV–AIDS prevention initiative in India ($200 million) provides education, treatment for sexually transmitted diseases, condoms, and clean needles and syringes in six states with high rates of HIV infection. A national HIV–AIDS treatment program in Botswana ($50 million) is currently treating about 56,000 patients and has provided valuable lessons about scaling up HIV treatment. The foundation has also given $528 million for AIDS-vaccine research and $124 million for research on a microbicide to prevent sexual transmission of HIV. In August, it announced a 5-year, $500 million grant to the Global Fund to Fight AIDS, Tuberculosis, and Malaria, bringing its total contributions to the Global Fund to $650 million and its total funding for HIV–AIDS programs to about $2 billion.

Ten projects in malaria-vaccine development are being supported ($258 million) through the Malaria Vaccine Initiative of the international, nonprofit Program for Appropriate Technology in Health; one vaccine will soon be tested in a large phase 3 clinical trial in Africa. The first comprehensive national effort by a sub-Saharan African country to control malaria with the use of drugs, insecticide-treated bed nets, and other methods is being supported in Zambia ($35 million). The foundation is also supporting the development of better tuberculosis vaccines, including a genetically engineered, more immunogenic version of the bacille Calmette–Guérin (BCG) vaccine, which researchers hope to test soon in large clinical trials in Africa and India.

More than 20 million mothers and infants have received basic health services through $110 million in grants for Saving Newborn Lives (a Save the Children initiative).

Africa in the early 1990s opened the couple's eyes to the vast health disparities between rich and poor countries. Gates has credited William Foege, a former director of the CDC, with awakening him to the potential social impact of his money — particularly by suggesting that he read the 1993 World Development Report, which starkly quantified the toll of disease in developing countries. From infectious disease experts, the couple learned that an amazing number of lives could be saved for what seemed to them relatively small investments. "We really did think it was too shocking to be true," Bill Gates has said.[2]

Buffett, for his part, has long intended to give away most of his $44 billion fortune, but he only recently decided to do so while he is still alive. He also changed his mind about where to donate it, choosing the foundation established by Gates, his friend and bridge partner, rather than the Susan Thompson Buffett Foundation, named for his late wife. That shift reflects his business philosophy of investing in companies that have a track record, rather than reinventing the wheel. By serving on the board of the Gates Foundation, he will have some say in how the funds are spent, and he made his gift contingent on Bill or Melinda's remaining at the helm.

The doubling of the foundation's budget comes at a time of change in the leadership of its health program. Earlier this year, Tadataka (Tachi) Yamada was named president of the foundation's Global Health Program, replacing Richard Klausner. Yamada, a gastroenterologist and former chairman of internal medicine at the University of Michigan Medical School, previously headed research and development at GlaxoSmithKline, where he oversaw a budget of more than $4 billion and more than 15,000 employees. Although his staff at the foundation is much smaller — just over 100 employees — the Buffett gift offers unique opportunities both for tackling the health problems that are already being addressed and for broadening the foundation's mandate. Yamada, who had been on the job for only 10 weeks when I spoke with him, had been traveling to field sites and listening to ideas about how to spend the additional money.

"I project that we're going to be spending a little bit more than half [the foundation's annual awards] on global health," Yamada said. "My initial reaction is to do more of what we're doing — to do it more completely or better." The foundation has invested in the development of new vaccines, drugs, and diagnostic tests for malaria, tuberculosis, HIV, and other infections, he noted, and some of these products will soon be ready for manufacture, large-scale testing, or distribution, requiring additional resources.

Yamada mentioned two new

areas that are likely to become foci of giving: health information and human-resource development. The improvement of health information systems could enable developing countries to quantify health problems, helping them to set spending priorities, improve health care delivery, and measure the effects of interventions. Yamada recently saw an impressive model program in Manhica, Mozambique, created in cooperation with Spanish epidemiologists. In the area of human resources, he said, the foundation is interested in worker-training projects that will improve health care delivery. "I'm not just talking about nurses and doctors; I'm talking about a broader array of health care workers with varying levels of education — down to community workers with very little," he said.

Some have urged the foundation to broaden its focus to include deadly noncommunicable diseases. Yamada said his program would like to become involved in efforts to reduce smoking and tobacco use in developing countries, perhaps by reinforcing initiatives for countries to sign the World Health Organization's Framework Convention on Tobacco Control, a treaty that will require signatories to increase taxes on tobacco products, ban sales to minors, regulate advertising, and take other measures.

When the Buffett gift was announced, some observers expressed concern that aid from other sources would decline because the Gates Foundation would be perceived as rich enough to solve the developing world's health problems. But experts say that the foundation's actions have consistently led to increased funding from others. "Without Bill Gates, we would never have had the Global Fund," said Kim. "And for sure, there would be no PEPFAR," the President's Emergency Plan for AIDS Relief.

In the area of malaria control, the size of the foundation's grants has enabled it to energize research and forge partnerships among academia, governments, and industry much more effectively than other institutions have, said Brian Greenwood, a professor at the London School of Hygiene and Tropical Medicine. Companies have been induced to develop drugs or vaccines for use in poor countries, because the foundation helps to pay the cost of development. "They have the potential to direct the overall pattern of what happens" in a field, Greenwood said. Critics have argued that such power to set the agenda has a downside. The foundation's grant making may not always reflect the priorities of recipients in developing countries, and its choices may influence the decisions of other funding agencies, potentially steering money away from basic science and toward product development. However, the Gates Foundation's wealth and independence allow it to take risks that could yield big payoffs. "Governments cannot afford to fail in the same way," noted Harvey V. Fineberg, president of the Institute of Medicine.

The history of the Global Alliance for Vaccines and Immunization (GAVI) illustrates both the dramatic progress that has been made and the continuing challenges. In the 1990s, childhood immunization rates with basic vaccines had stopped increasing in developing countries, and newer vaccines against diseases such as hepatitis B and *Haemophilus influenzae* type B were unavailable. Bill and Melinda Gates were attracted to a problem that might be attacked with money and technology; a $750 million Gates grant jump-started the alliance, and the foundation received a seat on GAVI's governing board. "Its intellectual input was critical," said Julian Lob-Levyt, president of GAVI. "I think the results-based nature of GAVI, which comes from Gates, is new in the development community."

GAVI now has almost $3.5 billion in commitments from governments and private sources, as well as $4 billion in long-term commitments to a new sister institution, the International Finance Facility for Immunization. In a financing innovation, pledges of future donations will be used to issue bonds on the financial market, allowing money to be spent up front to improve delivery systems, purchase vaccines in larger quantities, and assure manufacturers of a stable long-term market. Although Lob-Levyt predicts that financial incentives will attract new manufacturers and increase competition, lowering prices, the high cost of some vaccines remains problematic. In many countries, a weak health care infrastructure also represents a formidable barrier, so GAVI and the Gates Foundation have shifted course to address that underlying problem.

The Gates Foundation is still evolving, and its leaders acknowledge having made mistakes. For example, some early grants did not cover operating expenses for grantees; now they are included. The foundation staff underestimated the complexity of tasks such as delivering childhood vaccines in developing countries and found

that in some cases, 5 years of funding for projects was not long enough to deliver results. Although the foundation is known for its "lean" structure, some grantees said that current staff levels are barely adequate to handle the existing workload, and Yamada said that it will have to grow in order to double its spending. Choosing worthy recipients, monitoring projects, and measuring their effects will be especially challenging. "For our largest grants, GAVI and the Global Fund, we know the results that they've produced and they're pretty substantial," said Yamada. "For others, it's harder to measure . . . [but] we're beginning to get some evidence." In Botswana, for example, where the foundation supports a national HIV–AIDS testing and treatment program, the prevalence of HIV infection among girls 15 to 19 years of age decreased by 22% between 2003 and 2005.

Perhaps the Gates Foundation's greatest influence derives from its assumption that intractable problems can be solved, given enough money and international cooperation. For example, as a condition of receiving $287 million in grants for AIDS-vaccine research that were announced in July, 165 scientists in 19 countries will have to share their data in a central repository. Yamada predicted that such collaboration will become more common in the future, even in industry.

"We're trying to deal with very difficult problems that people are suffering from in the developing world," he said. "The more information sharing there is, the more patients will benefit."

Dr. Okie is a contributing editor of the *Journal*.

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FOCUS ON RESEARCH

Fingolimod and Sphingosine-1-Phosphate — Modifiers of Lymphocyte Migration

Steffen Massberg, M.D., Ph.D., and Ulrich H. von Andrian, M.D., Ph.D.

Related article, page 1124

Multiple sclerosis is considered an autoimmune disease in which CD4+ T cells and macrophages destroy oligodendrocytes, which synthesize and maintain axonal myelin sheaths in the central nervous system (CNS). This misguided attack results in progressive focal demyelination that can cause severe neurologic disability. In this issue of the *Journal*, Kappos et al. (pages 1124–1140) report that the immunosuppressant fingolimod (also called FTY720 or 2-amino-2-(2-[4-octylphenyl]ethyl)-1,3-propanediol hydrochloride) exerted considerable therapeutic effects in a small, placebo-controlled clinical trial involving patients with relapsing multiple sclerosis. Patients who received oral fingolimod once daily had a rapid reduction in disease activity, reflected in significant reductions in the relapse rate and in the number of CNS lesions found on magnetic resonance imaging. Patients who initially received placebo also had improvement after switching to fingolimod.

Studies of the pathogenesis of autoimmune encephalomyelitis in an animal model resembling human multiple sclerosis have uncovered an essential role of T-cell migration between the blood and two anatomical compartments, the CNS and the lymph nodes.[1] The disease is thought to be initiated in lymph nodes that receive lymph from the CNS. Here, oligodendrocyte-derived self-antigens are presented to T cells, which are constantly recruited to lymph nodes from the blood.

The majority of the T cells that recognize self-antigens are eliminated in their birthplace, the thymus, before they enter the systemic circulation. So in healthy persons, T cells that home to lymph nodes are either oblivious to any self-antigens that may be presented there or are not permitted to respond effectively. These naive T cells spend a day or less, on average, in the lymph nodes before they depart for the efferent lymphatics in the lymph-node medulla and then return to the blood. For reasons that are still poorly understood, patients with autoimmune diseases harbor T cells that can become activated by self-antigens.