

Instead of calling it environment and conservation, let's call it public health once in a while.

Angela Rooney

Environmental Quality and Social Justice in Urban America (1974)

PHARMACEUTICALS

Paying Attention to Neglected Diseases

Tropical diseases are drug development's poorest relations. Until recently, these diseases have been so ignored that "people even refer to them as neglected neglected diseases," says Charles Gardner, associate director for health equity with the Rockefeller Foundation, which funds a number of initiatives focused on diseases of the poor. In July 2003, a new international collaboration was launched to rein-vigorate research and development on treatments for tropical diseases.

The Drugs for Neglected Diseases Initiative (DNDi) was spearheaded by the volunteer medical group Médecins Sans Frontières (MSF) and five other partners: France's Institut Pasteur, the Malaysian Ministry of Health, Brazil's Oswaldo Cruz Foundation, the Kenya Medical Research Institute, and the Indian Council of Medical Research. The nonprofit initiative was designed to revitalize drug development as a public responsibility rather than a strictly market-driven enterprise.

Governments and the pharmaceutical industry are pitching in, with some already providing money (the European Union) and expertise (Merck & Company and

Novartis Pharmaceuticals). DNDi's operations, headquartered in Geneva, will be distributed throughout the developing and developed world, with the goal of supporting a budding collaboration on health care research and application between developed and developing nations.

DNDi is in the process of building a portfolio that will contain a balanced mix of short-, medium-, and long-term projects targeting neglected diseases. DNDi's initial drug development efforts are aimed at chloroquine-resistant malaria, human African trypanosomiasis (sleeping sickness), visceral leishmaniasis (also called *kala-azar*), and Chagas disease. According to the World Health Organization, malaria affects more than one-third of the world's population and kills more than 1 million children each year. Sleeping sickness afflicts half a million people and threatens more than 60 million in sub-Saharan Africa. Worldwide, about 12 million people suffer from visceral leishmaniasis, and 200 million are at risk of contracting it. Chagas disease afflicts an estimated 18 million in Latin America and threatens about a quarter of the region's population. All of these diseases are transmitted by biting insects. Chagas disease is also transmitted congenitally and through transfusion with infected blood.

Tropical diseases can be very difficult to treat, says Martin John Rogers, a program officer with the Parasitology and International Programs Branch of the

National Institute of Allergy and Infectious Diseases, because of the disease progression within human beings. Initial symptoms are often nonexistent, minor, or nonspecific, and by the onset of severe symptoms—sometimes decades after infection—the disease is so far advanced that treatment is either futile or possibly fatal in itself. Moreover, drug delivery techniques and treatment regimens are often impractical in rural and/or impoverished areas, and patients may need to travel great distances, leaving their families and lands untended, to reach the nearest health center. DNDi hopes to investigate and develop less toxic, more effective, and more practical treatments adapted to patient needs.

The global burden of neglected diseases has increased, some say, because pharmaceutical companies are loath to spend money on unprofitable drugs. Furthermore, the first wave of tropical medicine was driven by the self-interest of colonial powers, according to Mohammed Hassar, director of the Institut Pasteur du Maroc in Casablanca. "The health of soldiers, the colonists, and the local population was vital for the success of the colonization," Hassar says. But when colonial powers withdrew, they also took their money, medical expertise, and concern about local conditions. In the post-colonial world, the countries where neglected diseases have made a comeback must pick up the slack. "I believe DNDi is a good start," says Hassar.

Early reactions from researchers are encouraging. By July 2003, when DNDi was established as a foundation, it had received 71 project proposals from its first call for letters of interest from the scientific community. Early next year, work will commence on selected projects. Says DNDi spokesperson Jaya Banerji, "The organization is still in the process of building its portfolio of drug research and development projects and will soon be issuing a second call for proposals aimed at its target diseases." The success of these projects depends on the collaboration of scientists across the world and will enable DNDi to achieve its vision of improving the quality of life and health of people suffering from neglected diseases in poorer countries. —Valerie J. Brown



Awake to the possibilities. A new initiative seeks to drive drug development for neglected diseases such as sleeping sickness.

ENVIRONMENTAL MEDICINE

An Affordable Antimalarial

In a blend of new and old, a plant-derived drug called artemisinin that the ancient Chinese used to treat fever is now being used effectively against drug-resistant malaria. When derived from the plant *Artemisia annua*, artemisinin costs about \$1.50 per adult dose—unaffordable in much of Africa, where most malaria deaths occur. But while naturally derived artemisinin is too costly for many malaria sufferers in developing nations, an elaborate genetic engineering project may offer hope for a more affordable artemisinin-based therapy.

According to the World Health Organization, malaria kills more than 1 million annually. The malaria parasite *Plasmodium falciparum* has evolved resistance to older medicines, and artemisinin and its derivatives are considered essential to fighting the disease.

In April 2003, the volunteer medical group Médecins Sans Frontières asked international donors to promote “rapid implementation of artemisinin-based combination therapy (ACT), a proven treatment that is being promoted by the World Health Organization.” ACT works by pairing artemisinin with traditional antimalarials that act by other mechanisms.

In a project reported in the July 2003 *Nature Biotechnology*, Berkeley professor of chemical engineering Jay Keasling and colleagues inserted 10 genes into the common bacterium *Escherichia coli*, creating a microbe that makes amorphaadiene, an artemisinin precursor that is easily converted to the drug. The transferred genes convert a chemical commonly found in *E. coli*, acetyl co-enzyme A, into amorphaadiene. Instead of enhancing the *E. coli* genes that normally produce amorphaadiene, the substitute pathway becomes a second, much larger source of amorphaadiene.

One key to success has been balancing the multistep biosynthesis of amorphaadiene

in the bacteria, says Keasling. Some intermediate compounds in the synthesis, including isopentanyl pyrophosphate (IPP), are toxic to *E. coli* at high concentrations. It's critical to carefully balance the genes that synthesize and utilize IPP to ensure that IPP is quickly converted to amorphaadiene before it kills the *E. coli*, Keasling adds.

The transformed *E. coli* produce about a gram of precursor—enough for one adult dose of treatment—per liter of solution. By fine-tuning the bacteria and perhaps adding more genes, Keasling hopes to reach 50 grams per liter. “If we were to get some high, but reasonable, yields, we could be producing one treatment for twelve cents,” he says.

The report is “a landmark paper,” says Jörg Bohlmann, an assistant professor in the Biotechnology Laboratory at the University of British Columbia. Instead of transferring just one gene, he says, Keasling moved enough genes to create an entire new metabolic pathway in *E. coli*, thereby raising the yield of the drug precursor. Plants, he

notes, are quite variable in their production of specific chemicals. “If the plant has the best production at a certain stage of development, or in a certain part of the tissue, or under certain environmental conditions . . . Keasling can now control the conditions of production in *E. coli*” to maximize yield.

The transformed bacteria may be useful against other diseases besides malaria, says Keasling. Artemisinin is one of roughly 50,000 isoprenoid chemicals that have evolved to fight pathogens and parasites in plants, microbes, and some marine organisms. Other isoprenoids include the flavoring menthol, carotenoids (useful for combating ultraviolet damage), and Taxol (an anticancer agent derived from the Pacific yew).

Keasling says the engineered *E. coli* could be further transformed to produce other isoprenoid chemicals: “A company could tweak the bacteria a bit, add any number of plant genes involved in the chemical of interest, and get pretty much any isoprenoid.” —David J. Tenenbaum



Concocting a cure. Researchers are using genes inserted into *E. coli* to synthesize a precursor of artemisinin, used to treat malaria.

Fish on Prozac

The U.S. EPA is in the process of deciding whether regulations are needed for pharmaceuticals in water supplies. Studies now coming through the research pipeline may help the EPA with its decision. In a study presented at the November 2003 annual meeting of the Society of Environmental Toxicology and Chemistry, Baylor University's Bryan Brooks determined that fluoxetine hydrochloride (the active ingredient in the antidepressant Prozac) excreted into the sewer system is accumulating in the tissues of bluegill caught in nearby Denton Creek. Waste treatment systems often are ill-equipped to remove such contaminants from sewage.



Healing Afghanistan's Environment

At the request of the Transitional Islamic Government of Afghanistan, an international team largely funded by the European Commission embarked in October 2003 on a program to promote environmental governance and support rehabilitation of Afghanistan's war-ravaged environment and famished population. The US\$5 million-plus, two-phase program will address priorities set in the country's national development budget and in UNEP's 2003 *Afghanistan: Post-Conflict Environmental Assessment* [see “Environmental Triage in Afghanistan,” *EHP* 111:A470–A473 (2003)]. The program will first focus on organizing and building capacity for a specialized environmental Afghan public administration. Beginning in 2004, phase two of the project will launch efforts directed toward strengthening the Department of the Environment, establishing protected areas, and integrating environmental education into Afghan schools and universities.

Burning Banned for Irish Hospitals

In response to concerns over health effects linked to air pollutants such as dioxin and mercury emitted during the incineration of hospital waste, the Republic of Ireland and Northern Ireland joined in September 2003 to require nonburning technologies for treating the approximately 9,500 tons of medical waste the two neighbors produce annually. The Joint Waste Management Board of Ireland signed a 10-year contract to have 95% of the two countries' hospital waste sterilized using steam-based systems, which work as effectively as burning and can be more cost-effective. The remainder—which includes biohazardous matter—will be incinerated abroad.



ehpnet

Humanitarian Resource Institute Emerging Infectious Disease Network

Through its communications and advocacy efforts, the nonprofit Humanitarian Resource Institute (HRI) coordinates international health and quality-of-life initiatives in a number of wide-ranging areas, and endeavors to foster multilateral cooperation among countries. One of HRI's program areas centers on building awareness of emerging infectious diseases. To do this, the institute has established the Emerging Infectious Disease Network, a collaboration of international medical, veterinary, and scientific experts who share information and engage in academic discussion. At <http://www.humanitarian.net/eidnet/>, HRI provides a ever-expanding collection of international information resources on the growing threat of emerging infectious diseases.

The introductory page of the section has a link to the HRI academic discussion platform, an online forum that provides access to briefings, educational materials, articles, and other resources on the subjects of agricultural and public health infrastructure protection. Interested parties must register online to access this forum. Access currently is limited to public health administrations, university research departments, government facilities, and military programs.

Under the In The Spotlight header of the introductory page are links to reference libraries developed for specific diseases including West Nile virus, foot-and-mouth disease, and transmissible spongiform



encephalopathies. These libraries contain comprehensive

lists of links to information on the tracking of these diseases in the United States, as well as to related news articles, webcasts, and other Internet-based media from public, international, and U.S. government agency sources. Also listed are links to the homepage of the Centers for Disease Control and Prevention Division of Health Care Quality Promotion and to the U.S. Department of Health and Human Services' GlobalHealth.gov website.

Under the Outbreaks: In The News header, visitors will find links to articles about biodefense and epidemiological tracking related to specific diseases including influenza, monkeypox, SARS, West Nile virus, and foot-and-mouth disease, which have recently been capturing headlines and public attention around the globe. The Also In The News section of this page features links to recent articles on related topics such as veterinary medicine and the threat of chemical and biological terrorism. Also included here are links to online courses developed for medical and veterinary professionals by HRI.

More general information related to emerging infectious diseases can be found at the bottom of the main page. The General Information section provides a list of links to federal and international health data resources including health alerts and advisories, the journal *Emerging Infectious Diseases*, and the homepage for the National Center for Infectious Diseases of the Centers for Disease Control and Prevention. Also within this section are links to the World Health Organization (WHO) Global Outbreak Alert & Response Network, the WHO Department of Communicable Disease Surveillance and Response, the *Weekly Epidemiological Record*, and other WHO resources. The General Veterinary Research & Publications section provides links to the websites of, among others, the World Organization for Animal Health and the U.S. Department of Agriculture Center for Emerging Issues. —Erin E. Dooley

A Cool \$30 Million Pledged for Russian Arctic

Russia's vast Arctic region is heavily polluted with heavy metals and spilled petroleum linked to the area's huge mining and fuel extraction operations, radioactive materials leaking from aging nuclear power plants, industrial chemical runoff, and other hazards. In October 2003, a coalition led by the London-based nongovernmental Advisory Committee on Protection of the Sea announced a new campaign to help restore the region with the aid of US\$30 million donated by international agencies and governments. Initially the campaign will focus on educating potential investors on investing in the development of bio-based technologies for cleaning up petroleum, mining waste, and radioactive materials. Supporters of the campaign hope to remediate abandoned military bases and to bring indigenous peoples into the project as stakeholders.



AIDS Crops Agricultural Output

The UN Food and Agriculture Organization (FAO) and Joint UN Programme on HIV/AIDS have announced the release of a landmark report on the toll HIV/AIDS is taking on agricultural output in developing countries, especially in sub-Saharan Africa, where most of the region's 30 million HIV sufferers live in agricultural areas and up to 80% of the population may depend on farming for their subsistence. According to the FAO, HIV/AIDS is depleting such regions of their agricultural labor force for generations to come. Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe are among the African countries hardest hit in their agricultural labor force and suffering the worst from what the FAO terms "food emergencies."

U.S. EPA Says ¡Hola!

In fall of 2003 the U.S. EPA introduced a six-week Spanish-language radio campaign to be aired throughout the U.S. and Puerto Rico on the Hispanic Radio Network, which boasts 162 station affiliates and the potential to reach 90% of the U.S. Hispanic radio audience. The campaign is part of the EPA National Hispanic Outreach Strategy to involve the Hispanic-American community in helping to clean up and conserve the environment. Segments, which will run during the network's *Planeta Azul* (Blue Planet) program, give steps communities can take to improve quality of life, with topics ranging from children's health issues to water conservation to pesticide use. The radio spots will be complemented with columns to be published in 90 Hispanic newspapers across the country.

