SUMMER 00

Lens

A New Way of Looking at **Science**

Is global health possible?

A PUBLICATION OF VANDERBILT UNIVERSITY MEDICAL CENTER

Lens –
A New Way of Looking
at **Science**

SUMMER 2006

VOLUME 4, NUMBER 2

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Cover: World in a Petri dish, with a colored scanning electron micrograph of HIV budding from the surface of an infected white blood cell making up the continents. Photo illustration by Dominic Doyle; photography by Dana Thomas. Image credit: NIBSC/Photo Researchers Inc.

We think we know the world.
Now, we must imagine it.

– CARLOS FUENTES

Lens **is published two times a year by Vanderbilt University Medical Center in cooperation with the VUMC Office of News and Public Affairs and the Office of Research.** ***Lens*****® is a registered mark of Vanderbilt University.**

Our goal: to explore the frontiers of biomedical research, and the social and ethical dimensions of the revolution that is occurring in our understanding of health and disease. Through our ***Lens*****, we hope to provide for our readers – scientists and those who watch science alike –different perspectives on the course of discovery, and to leave them with a greater appreciation of the technological, economic, political and social forces that guide it.**

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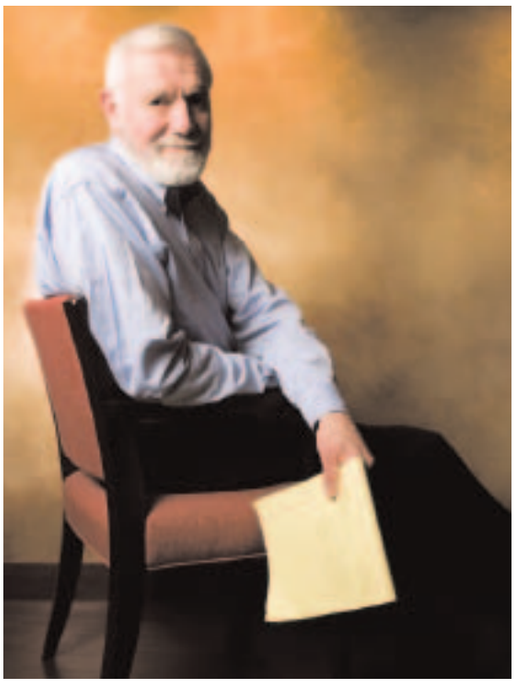

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ANNE RAYNER

Engaging in a world without borders

The importance of global health

By Sten H. Vermund, M.D., Ph.D.

Amos Christie Chair and Professor, Department of Pediatrics
Director, Vanderbilt University School of Medicine Institute for Global Health

Global health is a vibrant component of today's Vanderbilt. It is evident in the growing number of research partnerships with other nations that, for example, are providing AIDS treatment in Haiti, improving the care of premature babies in Colombia, and screening for diabetic retinopathy in remote areas of Peru and Bolivia.

It was evident in last year's creation of a new Institute for Global Health by medical school Dean Steven Gabbe, M.D. During a recent visit to Niger, where their son was posted in a remote rural village for his Peace Corps service, Gabbe and his wife, Patricia Temple, M.D., professor of Pediatrics, became convinced that Vanderbilt needed to be even more active in promoting health on a global scale.

It is evident in the international health component of the innovative "Emphasis Program," which allows first- and second-year medical students to pursue research and scholarship outside the classroom. Under the guidance of Peter Wright, M.D., director of the Division of Pediatric Infectious Diseases, more than

Pictured right: A symbol of global health: insecticide-treated bed nets, like the one opened over this child's bed in Tanzania. "It's a marvelous appropriate technology for resource-limited settings," says Sten Vermund, M.D., Ph.D., who directs the Institute for Global Health at Vanderbilt.

Photo by Hugo Jaeggi for the Swiss Tropical Institute in Basel, Switzerland

20 students are tackling projects in a dozen countries this summer.

Second-year medical student India Fox Landrigan has just published a manuscript about her experience in polio eradication in northern India. The remarkable odyssey of Milton Ochieng' – who also has just finished his second year of medical school – is reported elsewhere in this issue of *Lens.*

Why do we highlight a global health agenda when the problems in Tennessee are so acute and the need is so obvious? One reason is that the lessons learned in health care abroad apply here at home, and vice versa.

Each year several of our faculty members in Emergency Medicine provide medical services and training for local health care providers all over the globe, from Peru and Zambia to the Ukraine. Their international expertise was put to good use last year in New Orleans following the devastation of Hurricane Katrina.

International health care also is provided by Vanderbilt faculty, staff and students through Nashville's Siloam Family Health Center, which serves refugees from war-torn Southern Sudan, Kurds from Turkey, Iraq and Iran, and immigrants from several Latin American countries.

About a decade ago, Wei Zheng, M.D., Ph.D., MPH, and Xiao Ou Shu, M.D., Ph.D., MPH, a husband-and-wife research team, initiated several large cohort studies among women and men in Shanghai. These studies – which Zheng and Shu have continued since joining the Department of Medicine – are teaching us about dietary risk factors for cancer and heart disease in this country.

A second reason for Vanderbilt's engagement in global health is that American industry and commerce is now operating in a global marketplace, surely a permanent shift. On a December 2005 flight to Beijing, I sat next to an employee of a Tennessee firm whose technical-support business to assist steel-making in China now rivals business done within the United States.

The Vanderbilt Traveler's Clinic serves hundreds of travelers going to developing countries for mission work, business, research, adoption, humanitarian relief or tourism. A global awareness of malaria, yellow fever, influenza and many other diseases helps keep American travelers and military personnel healthy.

A third reason for us to care about the global health agenda is the fact that we rely on our tropical and global health experts to address local emergencies and those of expatriate Americans, including diplomats, missionaries, business persons, military employees and many others.

West Nile virus, avian influenza ("bird flu"), HIV/AIDS, imported malaria near airports, the threat of dengue fever, and other emerging infectious diseases threaten U.S. citizens who may never leave their hometowns. We need our global health experts to anticipate, prevent and confront these threats.

The U.S. military has been a fount of tropical disease expertise; I have just spent a year on an Institute of Medicine committee studying the infectious disease problems of returning troops and veterans of the Gulf War (Kuwait), Operation Enduring Freedom (Afghanistan), and Operation Iraqi Freedom (current war). Bullets and bombs are not the only threats to American servicemen and women overseas and veterans returning home.

Global health experiences also can be transformative for the next generation of American physicians. Some of my former medical students returned from abroad to take up similar challenges in this country: delivering health services to remote Inuit communities in Alaska; practicing in a rural hospital in the mountains of Puerto Rico; joining the Indian Health Service Corps in the Four Corners area of the Southwest; and working in Appalachia, Alabama's Black Belt region and the Mississippi Delta.

Several Vanderbilt alumni and faculty of both the School of Medicine and School of Nursing have served or are serving as medical missionaries. An example is Carol Etherington, M.S.N., assistant professor of Nursing, who is past president of the U.S. board of Médecins Sans Frontières (Doctors Without Borders).

Other alumni work as military physicians or as public health experts in the U.S. Centers for Disease Control and Prevention. Senate Majority Leader William Frist, M.D., on leave from his Vanderbilt faculty position, has been instrumental in spearheading HIV/AIDS treatment programs in Africa.

Enjoy this special issue of *Lens*. It shares the stories of faculty members at Vanderbilt and Nashville's Meharry Medical College who are leaders in the global health arena. Many of us have been inspired by the research and training partnerships in neonatology with Sweden and South Africa that were established by Mildred Stahlman, M.D., nearly half a century ago.

These commitments and contributions reflect Vanderbilt's broader vision: to prepare our students and engage our staff and faculty in research and service that is of vital importance to the future of our world in the 21st Century. **LENS**

ONE BUCKET AT A TIME

The transformative impact of global health

By Stephen Doster

When the residents of Lwala, Kenya, raised $900 for a one-way ticket to send Milton Ochieng' to college in the United States, they could not have envisioned that he would return to build a medical clinic in the heart of their rural village near the shores of Lake Victoria.

"They sold goats, cows, whatever they could to send me to America," recalls Ochieng', who this spring completed his second year at Vanderbilt University School of Medicine.

Since he arrived at Vanderbilt, Ochieng' has stirred considerable interest in his project among students and faculty across campus. This summer, three Vanderbilt students plan to work on various research projects in Lwala.

The office of medical school Dean Steven Gabbe, M.D., and the school's new Institute for Global Health are supporting his venture, as is the Vanderbilt Office of Active Citizenship and Service, which organizes service projects for undergraduates.

Ochieng' also has attracted the attention of Columbia University economist Jeffrey Sachs, Ph.D., who directs the United Nations Millennium Project to eliminate "grinding poverty, hunger and disease."

"Spend your summers in the Vanderbilt 'Millennium Village,'" Sachs urged students attending a recent videoconference on the Vanderbilt campus. "This is your generation's challenge. If you want to end this kind of suffering and poverty, you need to take the lead in this."

The story of Milton Ochieng' illustrates how global health is transforming the next generation of doctors, scientists and citizens in the United States.

"Lwala has captured our imagination because here is a Vanderbilt student who's creating this in his own home village," says Sten Vermund, M.D., Ph.D., founding director of the Institute for Global Health. "That's not done every day ... For the university community to come together in support of this is kind of exciting.

"But let's be realistic," he cautions. "We do not have a donor for this project. We are building a clinic with indigenous products at very little cost … The greatest challenge will be funding for staffing and consumables, namely supplies and drugs.

Pictured left: At left, Dennis Ojuki fetches water from a puddle to do his laundry in Lwala. The lack of running water is only one of the daunting challenges Vanderbilt medical student Milton Ochieng' must overcome to complete his village's first medical clinic, above.

Photos by Milton Ochieng'

"In the absence of funding, it will be hard to see this dream come to fruition."

Ochieng' – whose last name is apostrophized in his native language – is not dissuaded. He has overcome impossible odds before.

Ochieng' is a courteous, attentive and respectful young man with the body of an athlete. When he speaks, it is with well-considered words in a moderate tone.

His easygoing manner belies the harsh realities of his homeland. Given a chance to describe his world, his passion to help his village becomes immediately apparent – and infectious.

GRIM STATISTICS

The remote three square kilometers of Lwala village in western Kenya – more than a mile from the nearest highway – are home to approximately 1,500 people, mostly subsistence farmers.

Poor physical infrastructure, lack of electricity, and lack of reliable drinking water present dramatic challenges, but basic infrastructure is a minor concern compared to the village's healthcare needs.

During the two annual rainy seasons, the village is virtually cut off from the outside world. The nearest medical facility is seven miles away and provides only basic clinical services. Patients with acute illnesses or injuries must seek treatment at government hospitals in Kisii or Homabay, each 25 miles from the village.

Milton recalls one instance in which a pregnant mother experienced complications during labor. "Her relatives put her in a wheelbarrow and pushed her to get to the main road to the hospital, but she hemorrhaged to death before they reached the highway," he says. "Unfortunately, the unborn baby died in the womb too."

A high incidence of HIV/AIDS, malaria and other diseases contributes to a significant infant, child and adult mortality rate.

"These students … have grown up in (diverse) communities. They have high-school exchange programs and summer field trips abroad … It's a globalized world now."

Nationally, 7 percent of Kenyans have HIV/AIDS, but the HIV infection rate for the Nyanza Province, where Lwala is located, is closer to 30 percent.

The infant mortality rate in Kenya is about 120 deaths per 1,000 children – 15 times the average rate in the United States.

Ochieng's own parents reflect another grim statistic: the average 50-year life expectancy in Kenya.

His father, Erastus, passed away last year at the age of 55 from tuberculosis complicated by HIV infection. His mother, Margaret, a diabetic, died in 2004 at the age of 47 from AIDS-related pneumonia, complicated by typhoid fever and malaria. They had no access to anti-retroviral therapy.

Of the 408 children in the Lwala primary school (grades 1-8), nearly a third has lost one or both parents.

Ochieng' attended primary school in Lwala and performed well enough on the national exam to be admitted to the prestigious Alliance High School in Kikuyu, near the capital of Nairobi.

There, he learned about Dartmouth College through Alliance High alumni and became further interested after attending Brooks School in Andover, Mass., through a high school exchange program.

In 2002, as an undergraduate at Dartmouth, he helped build a health clinic in Nicaragua.

"A lot of what I saw in Nicaragua were the same things I see in Kenya in terms of poverty and lack of access to primary health care," he says. "Being part of a team that left a lasting impact on a community made me realize that maybe it would be something good to do in my own village."

When he began applying to medical schools, Ochieng' looked for a place that had a global health focus. "As I was interviewing with Vanderbilt, I found out about the Emphasis Program, which got my attention," he says.

OVERWHELMING NEED

The Emphasis Program provides students with the opportunity to pursue a variety of research and scholarly activities – from biomedical informatics to medical humanities – during the first two years of medical school. Among the most popular options: international health.

"These students have been brought up thinking it's a world of global interaction," explains William Schaffner, M.D., chairman of Preventive Medicine at Vanderbilt who for many years has been involved in international health.

"They have grown up in communities that are diverse. They have high-school exchange programs and summer field trips abroad … It's a globalized world now."

"I'm seeing more students who want to enter the global health field for the long-term," adds Peter Wright, M.D., chief of the Division of Pediatric Infectious Diseases, who leads the international health emphasis focus area. "In fact, it was the students who initiated the international health component … This wasn't something we envisioned."

For his Emphasis project, Ochieng' wants to establish a rural health clinic that will provide sustainable, accessible and affordable health care to the villagers of Lwala and surrounding area. He hopes the clinic will be able to offer other services such as HIV/AIDS education programs, tuition assistance for secondary schooling, and physical infrastructure development.

"One of the things we want to do once the clinic is up and running," he says, "is to conduct voluntary counseling and testing to find out what the exact HIV prevalence is for Lwala, and how to get the message out for prevention and treatment."

When Ochieng' presented his proposal to his village, the entire community responded enthusiastically. A council comprised of 21 elders was formed to oversee activities related to the clinic's construction and funding. Several families offered to donate land.

The local soccer club, along with Ochieng' and his brothers, dredged sand

Vanderbilt's international "strategy"

Vanderbilt University is developing a new international strategy to enhance the exchange of people and ideas, the quality of the student learning experience and the pursuit of cutting-edge research.

"We're not saying faculty need to get more international," says Joel F. Harrington, Ph.D., assistant provost for International Affairs.

"Most of our faculty are already very international in the sense that they're very active in international conferences, they have collaborators from foreign universities, they work at foreign institutes, they publish in foreign journals, and so on.

"Instead, the goal is to remove all logistical barriers that hinder the exchange of information, the exchange of people … (to encourage) a kind of intellectual free trade."

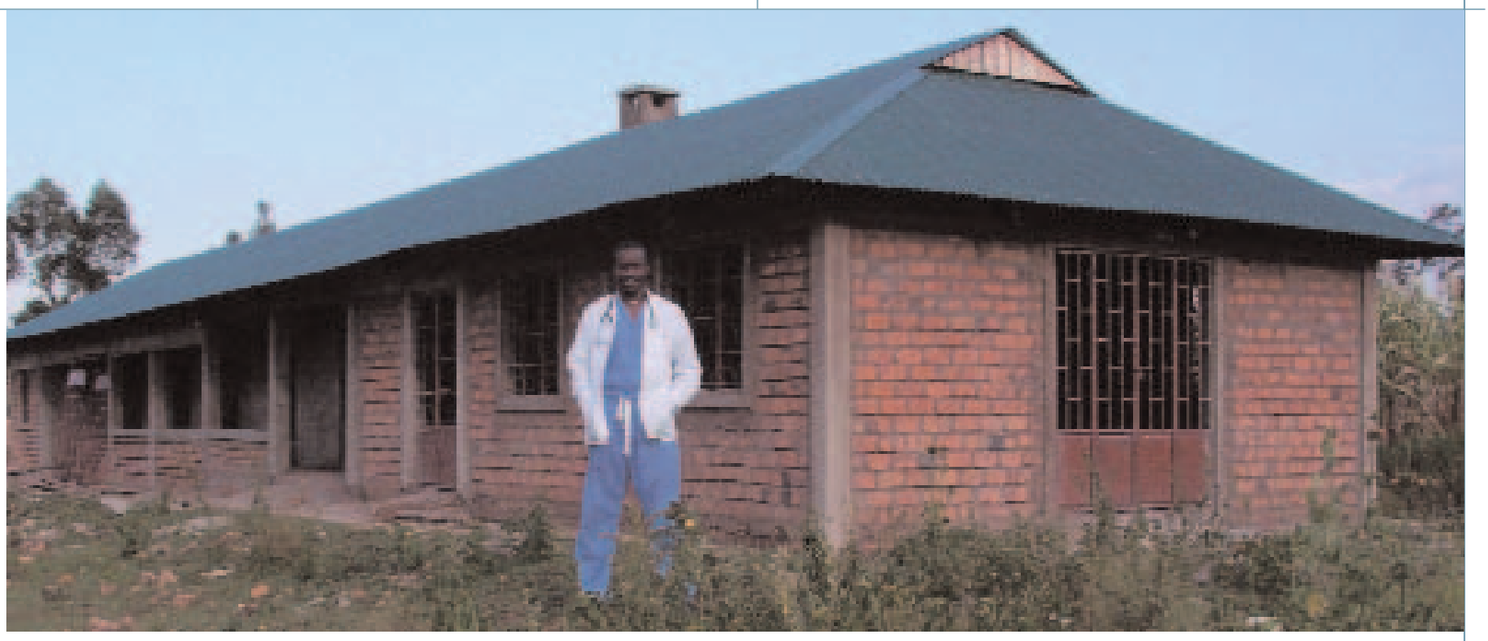
Harrington, an associate professor of History, is heading up the new Vanderbilt International Office, which will serve as a focal point for international activities.

The office is developing a Web site that will provide information for students interested in studying or working abroad, for faculty interested in international collaborations and for foreign students wishing to attend Vanderbilt.

In addition, an Advisory Council on International Affairs, representing faculty and staff from throughout the university, has been established to help develop "core international partnerships" with six universities by 2008. Currently under consideration: universities in Australia and South Africa.

Another goal is to allow Vanderbilt students to integrate their global experiences with their coursework and majors, perhaps by taking courses at universities in other countries or by participating in international service projects.

– BILL SNYDER



Second-year Vanderbilt medical student Milton Ochieng' stands in front of the first of three clinic buildings to be constructed in his village in Lwala, Kenya.

Village masons put up a wall to the first clinic building, completed late last year. Ochieng' will name the clinic for his late father, Erastus, a high school chemistry teacher who encouraged his son's audacious dream.

Photos courtesy of Milton Ochieng'

A team of villagers dredges sand from a nearby river to make the clinic foundation.

Ochieng' examines a child in his village, which is about 30 miles from Lake Victoria.

"It was a real culture shock. I realized that on my worst day … I live like a king compared to most of the world."

from the nearby river – one bucket at a time – for foundation sand and mortar. Bricks were manufactured locally, and rocks that serve as a foundation base were collected by locals and hauled to the site using ox-drawn carts.

Ochieng's plan calls for a three-phased construction. A building that houses a dispensary, laundry and patient treatment rooms has already been completed. Phase II will include a maternal child health care center and doctor's office. A building that houses separate wards for men, women and children will complete Phase III.

While drumming up support for the clinic, Ochieng' was referred to Mark Dalhouse, Ph.D., who directs the Vanderbilt Office of Active Citizenship and Service.

While Dalhouse could not provide any funds up front, he accepted Ochieng's offer to visit Lwala last summer.

"This was a reconnaissance trip to inventory what we would need to do to make the project successful," he says. "I shadowed Milton for 10 days and met public health officials.

"For me it was a real culture shock. I realized that on my worst day in Nashville, I live like a king compared to most of the world. What struck me was the lack of infrastructure – water, electricity, terrible road conditions. But it gave me a better idea of the logistics needed."

Dalhouse quickly realized a number of obstacles would have to be overcome to make the clinic a reality. "One of the chief challenges facing this project is the lack of clean water at the clinic site," he says. "I saw children sick with malaria with no medication. The need I saw for medicine there is overwhelming."

GLOBAL POSITIONING

Meanwhile, demand among Vanderbilt students for international experiences was burgeoning. In 2005, only a few students responded to postings for volunteers to work on service projects abroad. "This year," Dalhouse says, "it was standing room only."

Because the Lwala clinic is not at a point that it can support a large-scale service project, Dalhouse and Gregory Barz, Ph.D., associate professor of Ethnomusicology, are taking about 20 students to Kampala, Uganda, this summer to work in a variety of clinics, orphanages and other settings.

Like the proverbial pebble-in-a-pond, however, the ripple effect of the Lwala Clinic project is attracting students from outside the medical school. Students, faculty and other members of the Dartmouth community have been raising money for the project, as has a a new Vanderbilt group – Students for Kenya.

This summer Diana Lemly, a Vanderbilt medical student, Rachel Weaver, a graduating engineering major, and Abbie Foust, a graduating neuroscience major, will travel to Kenya to conduct a needs assessment for the village.

"We'll be conducting a 'health survey,' which means going door-to-door to potentially hundreds of homesteads, asking questions about water sanitation, women's health care, and the family's health history," Foust says.

"We're also planning on passing out brief health surveys at a local market in order to reach as many people as possible. We'll be looking at prevalence rates of HIV/AIDS, malaria, childhood illnesses, child immunizations and maternal and newborn care."

The students will also establish GPS (Global Positioning System) mapping of the clinic, nearby water sources, and other institutions in the area like primary schools and health facilities so that their house-to-house surveys can be easily replicated.

"We'll map distinctive landmarks and houses," Foust explains, "so that other people can return later and repeat our research to assess the impact the clinic is having on the health of the community.

"I hope to walk away with a whole new appreciation of Africa and the work it takes to start a small clinic."

Ochieng' understands all too well the frustrations of trying to work in two worlds. In Lwala, even basic communication services can be frustrating. Contacting his older brother, Omondi, who oversees the clinic's construction, is often a challenge.

"If his cell phone battery runs down," Ochieng' relates, "he has to go to Rongo, seven miles away, to recharge it. He also has to go to Rongo to check e-mail, which doesn't work half the time. In that case,

A PRICE OF PROGRESS

For nearly a decade, Scott M. Williams, Ph.D., has been traveling to Ghana twice a year to explore the genetic roots of heart disease in African-Americans.

Compared to Caucasians, African-Americans have a significantly greater risk of developing high blood pressure. It's unclear whether they are more likely than whites to develop arterial thrombosis, the formation of blood clots that can trigger heart attacks and strokes.

Identifying genetic contributors to cardiovascular disease in African-Americans is difficult, in part because of the complex mix of genes they inherited from West African tribes, Europeans and Native Americans, says Williams, associate professor of Medicine, Pediatrics and Molecular Physiology & Biophysics at Vanderbilt.

To simplify the search for genetic factors that may contribute to thrombosis, Williams and his colleagues are comparing blood levels of two key clotting factors in populations that are relatively homogeneous, at least from a genetic standpoint: rural farmers and urban dwellers of Sunyani, in western Ghana; and residents of the Netherlands.

The researchers hope to identify genetic factors responsible for differences in the levels of clotting factors – and the incidence of thrombosis – in the two groups. "Then you can use the information from that to try to get a handle on the African-American population, which is much, much more complex," he says.

Collaborators include Douglas Vaughan, M.D., and Nancy Brown, M.D., at Vanderbilt; Kwabena Adu Poku, Ph.D., MPH, at the University of Ghana; and Wiek van Gilst, Ph.D., at the University of Groningen in the Netherlands.

The study is relevant not only for African-Americans, Williams adds. As Ghana becomes more prosperous, heart disease is quickly becoming a major problem there as well.

– BILL SNYDER

Rethinking selenium

Nineteen years ago, Raymond Burk, M.D., took his first 12-hour-long train ride to a remote corner of southwest China to study a unique population of people whose diets are deficient in the essential mineral selenium.

Because the soil in this area is low in selenium, so are the locally grown vegetables. Selenium deficiency contributes to a potentially fatal form of cardiomyopathy, an inflammation of the heart muscle called Keshan disease.

Until the connection between diet and Keshan disease was established in the 1970s, people in this region "were just scared to death," says Burk, professor of Medicine and Pathology at Vanderbilt.

"It was sort of like polio in the U.S. back in the '40s and '50s," Burk says. "People tried to keep their kids from going to swimming pools … In the affected areas of China, they would send their children to live in areas where this disease did not occur."

The incidence of Keshan disease has declined among the 325,000 residents of Mianning County in the foothills of the Tibetan Plateau, thanks to the importation of selenium-rich vegetables from neighboring regions.

Yet selenium deficiency persists. Burk and Kristina Hill, Ph.D., research associate professor of Medicine at Vanderbilt, and their colleagues in China are trying to determine the best way to correct it through dietary supplementation.

The recommended dietary allowance (RDA) for selenium in the United States is based on the concentration of a blood "biomarker" called glutathione peroxidase. Another biomarker, selenoprotein P, may be more accurate, however.

Women of the Yi minority work in the rice paddies in Mianning County. Courtesy of Raymond Burk, M.D.

The researchers discovered that longer periods of supplementation are needed to raise selenoprotein P levels compared to glutathione peroxidase. Plasma glutathione peroxidase is likely a biomarker primarily for selenium in the kidney, they concluded, whereas selenoprotein P reflects selenium levels in the whole body.

While further study is needed, these results suggest that the RDA for selenium should be based on selenoprotein P, rather than glutathione peroxidase, the researchers reported last year.

Traveling to Mianning County is still no picnic, but Burk no longer has to spend 12 hours on the train – today he can fly to nearby Xichang.

– COLLEEN CREAMER

he has to go to Kisii or Homabay, 25 miles away, to check my e-mails."

Wright, who conducts AIDS research in Haiti, is well aware of the hurdles Ochieng' faces to make the clinic a reality. Yet he can't help being impressed.

"Milton has done much of the planning on his own," he says. "He's mobilized his village in Kenya and the Vanderbilt community …

"When Milton first approached me with the idea for his Emphasis project, it sounded impractical. But I've learned not to bet against him."

"Milton is a fireball," says Schaffner, "in a very organized, mature, goal-oriented way. One of the qualities of leadership is vision. He has a vision for health care in his country."

CHANGE THE WORLD

Like other global efforts, the Lwala clinic project raises cultural concerns – and opportunities. "All international medical activities have special challenges in that regard," Schaffner continues, "You also have to be careful that you're not creating problems when you introduce new things."

However, the culture also can be a source of education – on both sides of the Atlantic Ocean, says Barz, the ethnomusicologist.

Barz has studied ways traditional music can be used as a means to disseminate disease prevention and treatment information. In Uganda, such programs have had success in reducing the spread of AIDS.

"Lwala can draw on the Uganda model," he says, "by using historically-rooted modes of communication – song, dance, and drama troops – to spread health education messages in tandem with the medical model, which can consist of question-and-answer sessions, leaflets, and testimonials."

For Ochieng', the possibilities are just beginning.

Next fall, his younger brother Frederick – who already has logged long hours at the clinic – will join him at Vanderbilt as the second member of the Ochieng' family admitted to the School of Medicine.

"I want to use this experience to learn lessons about what works and what doesn't work in order to set up other clinics elsewhere," Ochieng' says. "I want to be able to work in the U.S. and in Kenya, half of the year in each place, so that once this clinic is up and running on its own, I can look for another similar project in another village or country.

"We want to get Vanderbilt involved as much as possible in the long term so that fourth-year medical students or residents can see what international health care entails."

Vermund is excited about the possibilities international education and research offers not only for future physicians but also for students in Vanderbilt's divinity, law and business schools, as well as those majoring in human and organizational development.

"Students will be impacted by what's going on – not just in Kenya, but in Uganda, Mozambique, the Sudan and other parts of the world," Dalhouse adds. "In the long term, (the Lwala clinic) project could be a template for student service experience, for faculty research, and for medical students interested in the developing world."

Barz puts it this way: "Students know they can't change the world. But their experiences abroad will change them, and that may eventually change the world they live in." **LENS**

Pictured right: Larry Zwiebel, Ph.D., and his weapon against malaria: a microscope used to study odorant receptors the malaria mosquito uses to locate her prey.

Photo illustration by Dean Dixon

tricking the mosquito's "nose"

A GRAND CHALLENGE TO COMBAT MALARIA

BY DAVID SALISBURY

Early in 2003, Larry Zwiebel, Ph.D., stepped out of a cab in front of a nondescript office building on the Seattle waterfront. It was an unlikely looking headquarters for an organization with billions of dollars at its disposal, but it was the address in the invitation he had received from the Bill & Melinda Gates Foundation.

Zwiebel, professor of Biological Sciences at Vanderbilt University, was among 30 "vector biologists" summoned to Seattle to advise members of a blue-ribbon scientific panel on a major new initiative they were planning.

Vector biologists study insects and other agents that spread infectious diseases. Zwiebel's "vector" is the *Anopheles gambiae* mosquito, which transmits malaria, and his goal is to understand the insect's olfactory system at the molecular level.

Six months earlier, Bill and Melinda Gates had decided to use the extraordinary resources of their foundation – some $27 billion – to make a major impact on global health, and to do so in an extraordinarily aggressive manner.

A major component of this effort would be a "Grand Challenges in Global Health" initiative to catalyze scientific breakthroughs against the diseases that kill millions of people each year in the world's poorest countries.

The initiative had been launched with a $200 million Gates grant to the Foundation for the National Institutes of Health (NIH), which fosters public-private partnerships to improve health through scientific discovery.

To ensure it got the biggest bang for its megabucks, a 22-member board of distinguished scientists chaired by Nobel laureate and former NIH Director Harold Varmus, M.D., had asked top experts in a number of related fields to come to Seattle for a brainstorming session.

"The atmosphere was almost somber," Zwiebel recalls. "They made it clear that this was a very important challenge, one that they took very seriously."

During the three-day meeting, Zwiebel and his colleagues were divided into working groups. Each group was asked to come up with a consensus set of suggestions. Board members apparently liked what his group had produced because many of its suggestions were incorporated into the final 14 "challenges" announced in October 2003.

The object was not simply to discover new knowledge, but also to create "deliverable technologies" – health tools that are both effective and practical. The tools should be inexpensive to produce, easy to distribute and simple enough for people in developing countries to use.

This approach struck a strong chord with Zwiebel. "Ever since … graduate school, I have wanted an opportunity to make a difference," he says. "I have nothing but love and admiration for basic science, but the idea of working toward a practical application is very satisfying."

So Zwiebel began rounding up his "dream team" of insect olfactory researchers to take advantage of this opportunity.

First, there was John Carlson, Ph.D., of Yale, an ongoing collaborator who had developed a method for transplanting the mosquito olfactory system into the intensively studied fruit fly *Drosophila melanogaster*.

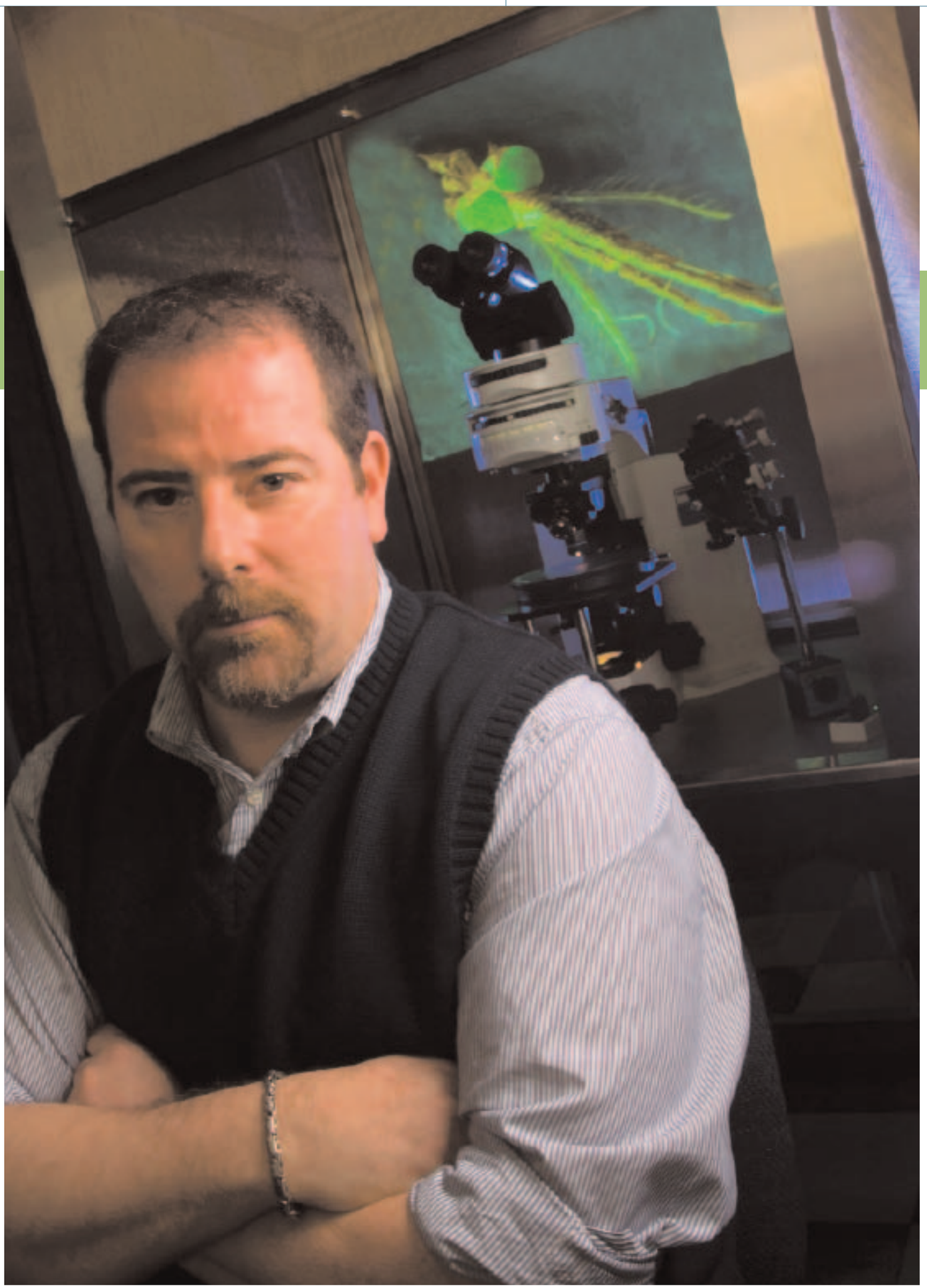
Next was Willem Takken, Ph.D., at Wageningen University in the Netherlands, who Zwiebel got to know while he was on a post-doctoral fellowship in Heidelberg.

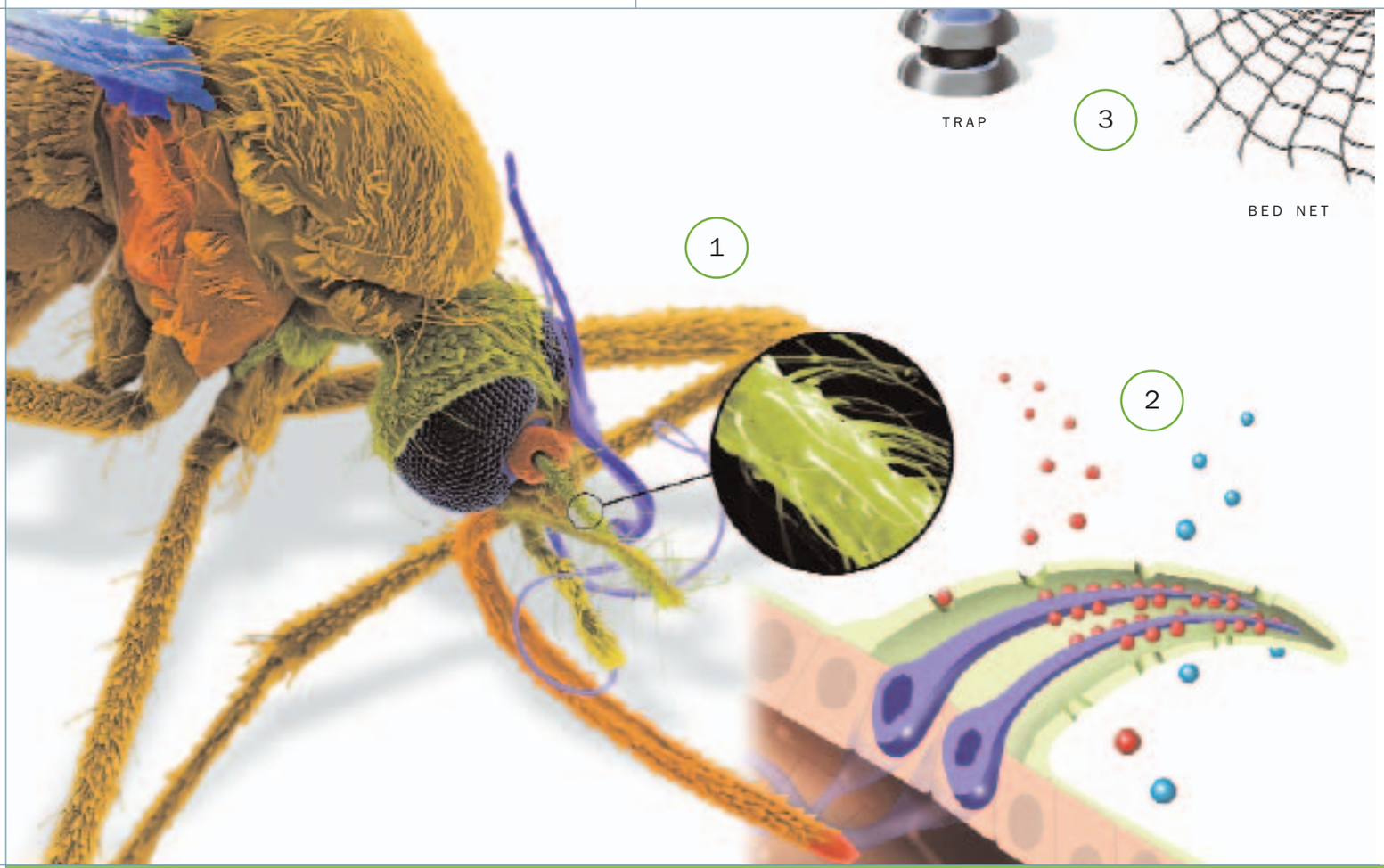
Takken, who is a leading expert on mosquito behavior, had extensive experience and contacts in Africa. He was instrumental in recruiting Gerry Killeen, Ph.D., from the Ifakara Health Research and Development Centre in Tanzania and David Conway, Ph.D., from the Medical Research Council Laboratories in The Gambia.

Deadliest animal

"Every one of the people who are involved, both the principals and the supporting scientists, have made critical insights and contributions over the last two decades. So, for me, it is really an honor to act as the coordinator," Zwiebel says.

The Seattle meeting was the beginning of what proved to be an extremely long and arduous process. At the end of 2003, the scientific board issued a request





How to trick the mosquito's nose

Malaria control at the molecular level

Mosquito image by Tina Carvalho, Pacific Biosciences Research Center, Honolulu. www.pbrc.hawaii.edu/microangela.

Illustration by Dominic Doyle

Step 1:
To trick the mosquito's "nose," scientists first have to find out how the insect "smells," in order to understand how it identifies its prey. They do this by scanning the mosquito genome for genes that encode odorant receptors, proteins found primarily in sensory hairs, called sensilla, on the mosquito's antennae. Some of these receptors bind specifically to chemicals found in human sweat. At least one receptor gene is expressed only in the antennae of the female mosquito. Only female mosquitoes bite humans, and the expression of this gene rises when they are "hungry" for a human blood meal.

Step 2:
The next step is to identify chemical compounds that bind to this and other mosquito odorant receptors. Inserting the mosquito genes into the fruit fly and other model systems makes them easier to study. Researchers were able to screen about 350 different aromatic compounds found in human sweat. One of them, 4-methylphenol, strongly activated the female-specific receptor. The scientists are now looking for other non-toxic compounds that attract, repel or simply confuse the mosquito's olfactory system. These compounds will be tested for their effect on the behavior of live mosquitoes.

Step 3:
Ultimately, the researchers hope to develop long-lasting combinations of synthetic compounds that either attract or repel the female mosquito. Repellants could be embedded in mosquito netting to prevent the insect from finding her sleeping human target, while attractants could be used to draw her to pesticide-containing "traps."

for letters of intent from research groups interested in participating, and received more than 1,500.

After reviewing these letters, the board invited 450 groups, including the Vanderbilt-led team, to submit proposals.

"This was the most extensive grant application I have ever been involved with," Zwiebel says. It took him and his colleagues several hectic months filled with international teleconference calls and thousands of e-mails to prepare their proposal.

"We were all exhausted when we finally submitted our proposal in June 2004," he recalls. "I felt completely drained but, at the same time, I felt that it was the best proposal that I had ever written and that we said exactly what we wanted to say."

Six month later, Zwiebel and his colleagues learned that their effort had been successful: Theirs was one of only 40-odd proposals selected for negotiations for funding. The negotiations continued for several months before the initiative announced, in June 2005, that it had offered 43 grants to support research into a broad range of innovative research projects.

The bulk of the money – $450 million – was provided by the Gates Foundation, with an additional $27.1 million coming from the Wellcome Trust of the United Kingdom and $4.5 million from the Canadian Institutes of Health Research. The three organizations jointly administer the initiative along with the Foundation for NIH.

The grants fell into several broad areas: developing improved vaccines to prevent diseases like malaria, tuberculosis and HIV; discovering ways to prevent the development of drug resistance; growing more nutritious crops to combat malnutrition; developing better methods for diagnosing and tracking disease in poor countries; and developing new ways to prevent insects from transmitting diseases.

Zwiebel's group received an initial grant of $8.5 million for five years to develop ways to disrupt malaria transmission by chemical manipulation of the malaria mosquito's sense of smell.

Theirs was one of seven grants that targeted the mosquito, reflecting the fact that the tiny insect is considered to be the deadliest animal on the planet. Malaria kills somewhere between 700,000 to 2.7 million people every year; two other mosquito-transmitted diseases – dengue fever and yellow fever – kill another 630,000. The World Health Organization estimates that a child dies of one of these diseases every 30 seconds.

"I was very impressed with the seriousness of the effort and the way they are trying to be circumspect in addressing what clearly are very complex issues," says Zwiebel.

"Malaria control is not going to be a unilateral process," he says. "We see vector control as one component in an overall multi-lateral strategy with more than one arrow … bed nets, vaccine development, vector control, water treatment, housing improvement – these are the elements that are going to bring malaria into a controllable strategy."

The arrow in the Zwiebel group's quiver is applying knowledge about how the mosquito's "nose" works in order to identify chemical compounds that act as "super-repellants" and "super-attractants."

The mosquito's "nose" is located in its antennae and other head appendages. Studies at Vanderbilt and elsewhere have shown that its olfactory system consists of an array of different odorant receptors, each of which responds to a very narrow range of chemical signals.

These findings suggest that it should be possible to identify the specific human odorants and their respective receptors that allow female mosquitoes to identify their hosts when they need blood to reproduce. They also raise the possibility of identifying other chemicals that interact with these receptors in combinations that either attract or repel these highly selective insects.

Super-repellants

Previous studies have shown that human sweat contains about 350 different aromatic compounds, but not much research has been done on them, so researchers do not know much about individual variations in these odorants. Recent evidence indicates that mosquitoes use a blend of many odorants in targeting prey. So the researchers realize that they are faced with deciphering a highly complex system.

To meet the challenge, Zwiebel and his colleagues are setting up an international research network that extends from Vanderbilt, Yale and the Netherlands to Tanzania and The Gambia. It is designed to identify odorants and the receptors that mediate attraction or repulsion to humans for *An. gambiae*, and then to use this information to try to reduce the transmission of malaria in areas where the disease is endemic.

The network begins in the high-tech genetic engineering and molecular biology laboratories at Vanderbilt and Yale, to identify chemical compounds that interact strongly with receptors in the female mosquito's antennae, and which appear to be related to host selection.

The mosquito's olfactory receptors are members of a diverse family of proteins called G protein-coupled receptors (GPCRs) that are embedded in the membranes of nearly every cell, and which are the most common conduit for signaling pathways found in nature.

Two thirds of all drugs used in humans target GPCRs. Pharmaceutical companies and academic medical centers like Vanderbilt have developed large-scale, high-throughput screens as part of their drug discovery programs to find small molecules that interact with them.

The Zwiebel group has joined forces with the drug discovery team at the

14 GRAND CHALLENGES IMPROVING HEALTH IN THE DEVELOPING WORLD

Create Effective Single-Dose Vaccines
Prepare Vaccines that Do Not Require Refrigeration
Develop Needle-Free Vaccine Delivery Systems
Devise Testing Systems for New Vaccines
Design Antigens for Protective Immunity
Learn About Immunological Responses
Develop Genetic Strategy to Control Insects
Develop Chemical Strategy to Control Insects
Create a Nutrient-Rich Staple Plant Species
Find Drugs and Delivery Systems to Limit Drug Resistance
Create Therapies that Can Cure Latent Infection
Create Immunological Methods to Cure Latent Infection
Develop Technologies to Assess Population Health
Develop Versatile Diagnostic Tools

From: www.grandchallenges.org

Vanderbilt Institute of Chemical Biology to identify novel sets of odorants that stimulate the mosquito receptors.

These compounds will be tested in the Carlson lab at Yale for their ability to activate olfactory receptors that have been transplanted into the fruit fly, the "lab rat" of genetic research as well as in the Zwiebel lab at Vanderbilt where they will be expressed in eggs of the frog genus *Xenopus*, and in defined cell-culture systems.

Because *Drosophila* has been so extensively studied for years, it provides a platform for studying mosquito receptors that is much easier than working with *Anopheles*. *Xenopus* and cell culture systems provide additional options as well as the ability to carry out high throughput screens for active molecules.

The most interesting molecules, which the researchers have dubbed BDOCs (Behaviorally Disruptive Olfactory Compounds), will be shipped to Wageningen University, where their effects on the physiology and behavior of individual mosquitoes will be analyzed. This information will be sent back to Vanderbilt and Yale to provide additional guidance in their search for candidate compounds using medicinal chemistry approaches.

BDOCs that pass the behavioral tests will be forwarded to Tanzania, where the researchers will combine them into different blends and evaluate how they affect laboratory-reared mosquitoes in a large biosphere that simulates the natural environment. They will also explore practical methods for producing these compounds from naturally occurring sources.

Finally, the most promising blends will be field tested in cooperating villages near Ifakara and in The Gambia by members of the research team. Compounds that are effective "super-repellants" could be embedded in mosquito netting to keep mosquitoes from finding their prey, while "super-attractants" could be placed in pesticide-laden traps.

The project's goal is to develop the first target BDOCs later this year, and deliver them for testing in Tanzania the next year.

Zwiebel and his colleagues decided to work on chemical interventions, as opposed to the genetic approaches proposed by some of their colleagues, in part because they feel that chemical methods will be adopted more readily by the people who live in the areas where malaria is endemic.

"There is a long history of chemical intervention and insecticides," Zwiebel says. "People have been slapping everything from mud to animal feces all over themselves for thousands of years to protect themselves from insect attacks.

"We are essentially bringing 21st century technology to a very well-established set of paradigms. I don't think we have to convince many people that developing new, safe, economically effective repellants is a good idea."

Surgical strike

Other Grand Challenges projects are pursuing genetic strategies to interfere with the ability of mosquitoes and other insects to transmit diseases. There are concerns, however, that development and release of transgenic insects may have unpredictable and undesirable ecological consequences.

In comparison, the Vanderbilt-led team is trying to target the mosquito's sense of smell with compounds that will have a minimal impact on the environment. "We don't have to worry about making an environmental faux pas with regard to releasing something that is never coming back," Zwiebel comments.

The potential of an olfactory strategy has been demonstrated by the use of scented baits to kill the African tsetse fly. The program, which has replaced the practice of treating large tracts of land with persistent insecticides, is widely considered to be an environmental and technological success.

"One of the concerns that we have from an ecological point of view is to only target the disease vector mosquitoes that we want to repel," says Zwiebel. "Many insects play critical roles in ecosystems in agricultural and other contexts that we do not want to affect unnecessarily. This can be potentially very devastating."

Instead, the researchers are focusing on the receptors they have characterized that are considerably different from those found in other insects. They figure that this gives them the opportunity to develop a "surgical strike capacity" that will target the *Anopheles* mosquito and leave all of the other insects alone.

"We are not talking about eradicating anything, and we are not talking about species replacement. We want to take as ecologically benign an approach as possible in order to reduce the contact between humans and *Anopheles* mosquitoes. That is where our interest ends," Zwiebel says.

Fortunately, he and his colleagues have plenty to work with. They have characterized 77 novel odorant receptors as potential targets. Not only does this increase the odds that they can find odorant blends which are highly selective, it also gives them an opportunity to eliminate the problem of resistance.

It hasn't taken mosquitoes long to develop resistance to many insecticides. That is because mutations in one or two genes are enough to make the chemicals ineffective.

The same would hold true for a repellent that acted on a single receptor. However, if the scientists can produce repellants containing a blend of compounds that stimulate a number of receptors, it is virtually impossible for the insects to develop resistance to them, Zwiebel says.

Although the Grand Challenge is focused on a practical outcome, Zwiebel expects it to yield new information about the molecular basis of behavior that could apply not only to insects but to other animals, including humans.

Researchers are now in a good position to understand peripheral elements of the olfactory system, such as how the mosquito senses the chemical environment at the extreme end of its nervous system, and how that chemical information – in mosquitoes and other insects – is translated into neuronal information.

"At the other end, we are also focused on the behavioral output," he continues. "What can we do to change an attractive behavior into a repulsive behavior? Is it a concentration effect? Is it a level of stimulation of the neurons?" These are some of the basic questions that the researchers hope to answer in the course of the project.

"The fact that we can use these tools to understand fundamental neuroscience questions while, at the same time, making an important contribution to global health issues … It's almost too good to be true," Zwiebel says. **LENS**

"We are not talking about eradicating anything … We are not talking about species replacement. We want to take as ecologically benign an approach as possible to reduce the contact between humans and … mosquitoes."

Thwarting a clever devil

Efforts to improve the TB vaccine

BY BILL SNYDER

A Vanderbilt-led team of researchers has developed a new vaccine technology that may prevent the spread of tuberculosis, a bacterial infection that kills more than 2 million people worldwide each year.

The technology has been licensed for further product development by the non-profit Aeras Global TB Vaccine Foundation.

With support from the Bill & Melinda Gates Foundation, Aeras is working as a "product development partnership" with public and private organizations around the world. The goal is to bring an improved TB vaccine to market within the next seven to 10 years.

Mycobacterium tuberculosis can hold out in the lungs of its victims for decades, effectively "walled off" by the immune system. When immunity is compromised by diseases like AIDS, the bacterium can re-emerge in a highly contagious form that can be spread to other people through coughing.

DANA JOHNSON

Douglas Kernodle, M.D., senior research specialist Cindy Hager (right), and their colleagues at Vanderbilt and the VA are now handing off the results of their labors to a non-profit foundation for development.

As a result, rates of active – and highly contagious – TB are skyrocketing in developing countries, especially those with a heavy burden of AIDS, says Douglas Kernodle, M.D., the David E. Rogers Professor of Medicine at Vanderbilt University Medical Center.

The current Bacillus Calmette-Guérin (BCG) vaccine is made using a related bacterium that has been weakened or "attenuated" so it cannot cause disease. The vaccine is given annually to 100 million newborns worldwide but provides inadequate protection against the pulmonary form of TB.

In the mid-1990s, Kernodle, Kathryn Edwards, M.D., professor of Pediatrics, and their colleagues at Vanderbilt and the Veterans Affairs Medical Center in Nashville began to study superoxide dismutase, an enzyme secreted by the TB bacterium in large amounts.

The enzyme "detoxifies" oxidants (reactive oxygen species) released by certain immune cells to kill foreign invaders. The researchers believed that TB "probably evolved high-level superoxide dismutase secretion as part of its strategy for infecting human hosts," Kernodle recalls.

Through a bit of genetic engineering, they were able to reduce secretion of the protective enzyme. When Kernodle's colleague at the Syracuse VA Medical Center, Michael Cynamon, M.D., infected mice with the impaired bacteria, the bugs were wiped out by the animals' immune systems.

Then, in late 2000, came Kernodle's "Eureka moment."

One of his colleagues, Markian Bochan, M.D., Ph.D., noted that superoxide dismutase can help rescue a cell from apoptosis, a type of programmed cell "suicide" that clears diseased or defective cells from the body.

"Then I got weak in my knees and chills down my spine because I realized that TB was pumping this (enzyme) out," Kernodle recalls. "Clever devil," he thought. "TB wants to live inside of a macrophage, so it is going to prevent that macrophage from committing suicide, and it's going to keep it alive."

The macrophage, a type of white blood cell, is the target of TB infection. The researchers realized that preventing apoptosis might also be the way the bacterium inhibits the immune system, thereby enabling it to cause a chronic infection.

If the infected macrophage fails to undergo apoptosis, then bacterial antigens – protein markers that ordinarily would trigger a more vigorous immune attack – would not get processed efficiently. In scientific terms, *M. tuberculosis* is able to evade "apoptosis-associated cross priming" of the immune system.

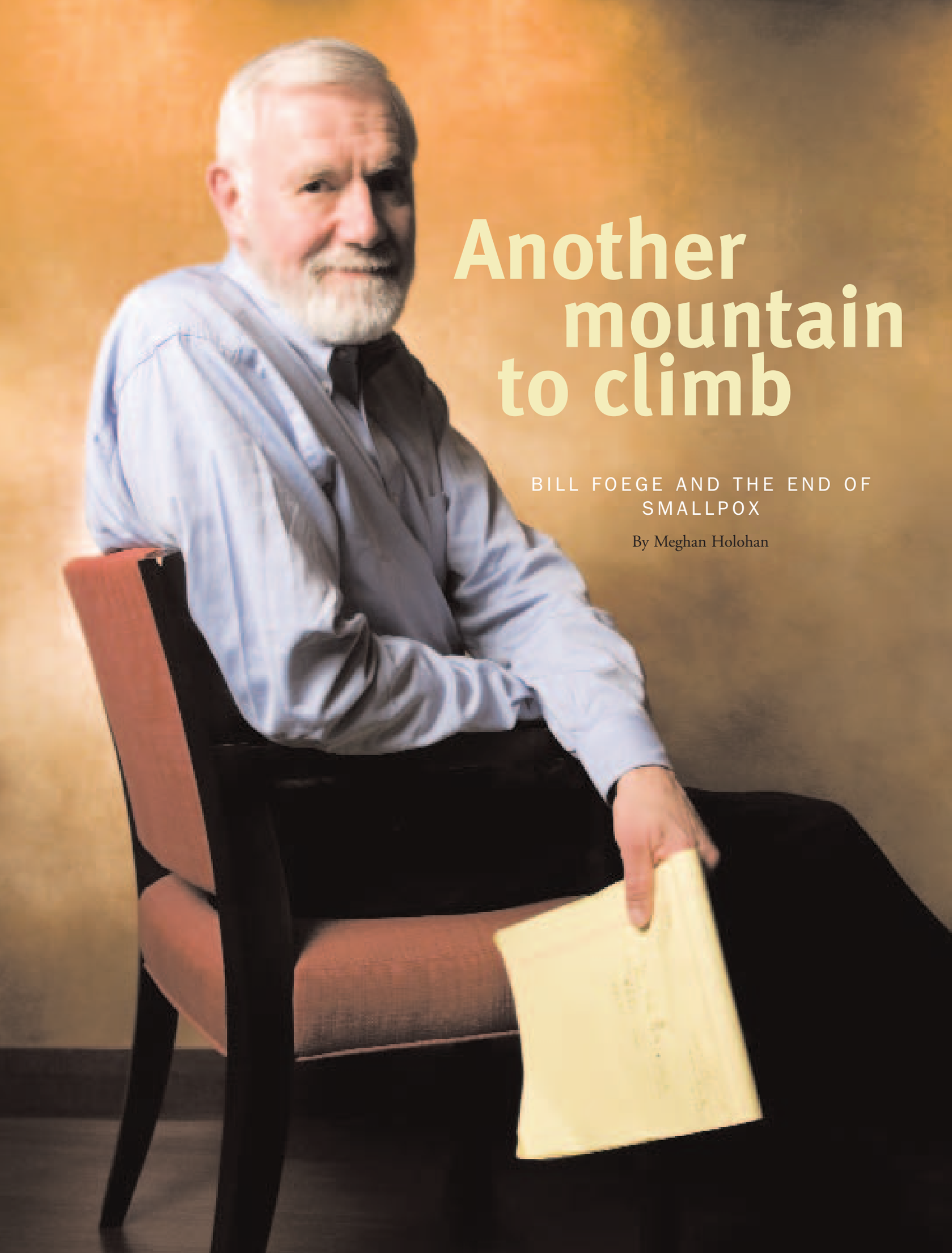
The researchers decided to see what would happen if they reduced the ability of the attenuated bacterium in BCG to produce superoxide dismutase and other anti-oxidant factors. Over the course of several years, with help from other investigators skilled in performing genetic manipulations, they stripped away successive layers of anti-oxidant factors from the vaccine as if they were peeling an onion.

The genetically engineered bugs have been progressively weakened in such a way that they can no longer prevent the death of the macrophages they inhabit or the resulting cross priming of the immune system.

"It's this broader repertoire of immune responses that you need to 'melt' (the infection) away and get rid of it for good," Kernodle says. "And that's the kind of responses now that we're getting (in animals) … with progressively more potent vaccines."

Under the licensing agreement announced this spring, Aeras will use the technology to modify BCG and will shepherd the new vaccine through clinical trials toward FDA approval. The foundation has developed field sites for testing near Bangalore, India, and Cape Town, South Africa.

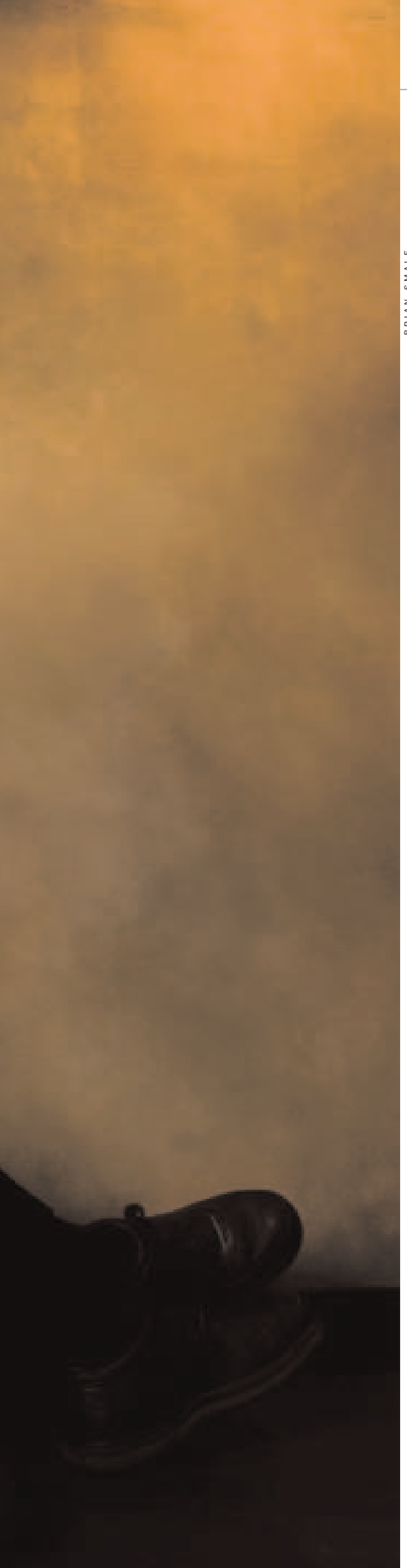
"Currently one-third of the world's population is infected with TB, and every second, one more person is newly infected," says Foundation President and CEO Jerald Sadoff, M.D. "A new vaccine is the best hope for defeating this terrible disease." **LENS**



Another mountain to climb

BILL FOEGE AND THE END OF SMALLPOX

By Meghan Holohan



BRIAN SMALE

One day in 1966, the two-way radio in the corner of the medical clinic crackled: "Can you come see if there is a smallpox case in the village?" William "Bill" Foege, M.D., MPH, jumped into his VW bug and bumped over the dirt plains of eastern Nigeria where he was serving as a medical missionary until he got to the village. Sure enough, it was smallpox.

At the time, public health experts thought the best way to rid the world of this ancient, often-lethal scourge was to vaccinate everybody. But Foege (pronounced "Fay-ghee") didn't have enough vaccine for everyone in the village.

As a consultant for the smallpox eradication program operated by the U.S. Communicable Disease Center (now the Centers for Disease Control and Prevention), he also knew blanket vaccination wasn't foolproof. Sometimes public health workers only went to certain locations like schools to give shots. Sometimes they vaccinated the same students over and over again.

Was there another way?

Foege imagined himself as a smallpox virus. To jump from one person to another generally required close, prolonged contact. But what if the close contacts had already been vaccinated? Could the virus be stopped?

Perhaps, but first he had to find everyone suffering from smallpox.

So Foege, the lanky, gregarious son of a Lutheran minister, called local missionaries via two-way radio (there was no telephone service), and asked them to recruit a network of "runners" to canvas the villages in their areas.

The runners carried photographs showing the small and rubbery smallpox lesions. They asked children too young to answer anything but the truth, "Have you seen anybody who looks like this?" Small boys and girls proudly pointed to the homes where smallpox sufferers lived.

Foege and his team then moved in to vaccinate their contacts – a technique now known as surveillance and containment or circle vaccination – and village by village, smallpox began to disappear.

"He was charming. He was persistent. He was intelligent. He was analytical," says longtime friend and colleague William Schaffner, M.D., chair of Preventive Medicine at Vanderbilt University Medical Center. "And so he created this new approach – the find-and-contain through ring immunization, interrupting the chain of transmission strategy of smallpox eradication.

GRAND CHALLENGES – A CRITIQUE

Like any ambitious endeavor, the Grand Challenges in Global Health initiative has its share of skeptics.

Last August in *The Lancet*, Anne-Emanuelle Birn, Sc.D., associate professor of Public Health Sciences at the University of Toronto, criticized the initiative for a "narrowly conceived understanding of health as the product of technical interventions divorced from economic, social and political contexts."

"Global health," she wrote, "might be better served through political support for universal, accessible and comprehensive public-health systems … in the context of overall improvements in living and working conditions."

"I believe the approach is wrong," added David McCoy, B.Med., DrPH, managing editor of *Global Health Watch*, in a story published last September in *RealHealthNews*.

"They will develop vertical programs from which some people will benefit," McCoy said, "but I doubt that there will be anything sustainable. I doubt if they will build the health care infrastructure for the poor countries."

Microsoft Chairman Bill Gates, in a speech to the World Health Assembly in Geneva in 2005, defended the initiative's emphasis on research.

"Some point to the better health in the developed world and say that we can only improve health when we eliminate poverty. And eliminating poverty is an important goal," Gates said. "But the world didn't have to eliminate poverty in order to eliminate smallpox – and we don't have to eliminate poverty before we reduce malaria.

"We do need to produce and deliver a vaccine – and the vaccine will save lives, improve health and reduce poverty," he continued. "… When health improves, life improves by every measure."

Ann Marie Kimball, M.D., MPH, professor of Epidemiology at the University of Washington, told the *Seattle Post-Intelligencer* that Gates' approach certainly can be debated, but "the fact that these investments are being made is extraordinarily important."

Since 1995, the Bill & Melinda Gates Foundation has awarded nearly $6 billion in grants to support global health services and research.

– BILL SNYDER

"That's not laboratory science," Schaffner continues, "but that conceptual innovation led to the eradication of one of the greatest plagues that mankind has ever known. That's public health."

Forty years ago, when Foege and his young family shared a four-room mud hut, he and his wife, Paula, made sure their 3-year-old son David wore shoes so he wouldn't get hookworm. The child had received every conceivable vaccination before he left the United States. They boiled their water and slept under mesh mosquito nets.

Foege realizes that if he'd had to survive on the average Nigerian's income – less than a dollar a day – he would have spent his money on food instead of vaccinations and mosquito nets.

It's this knowledge – 27 years after smallpox was eradicated from the Earth – that keeps him focused on improving public health worldwide. He can't get away from it.

"He has a tremendous sense of compassion and humanity, and his vision is based on intellect and experience and his understanding where things fit," says another longtime colleague, James Curran, M.D., MPH, dean of the Rollins School of Public Health at Emory University and former director of the CDC's AIDS Task Force.

"He has a tireless commitment of improving public health of underserved," Curran says. "He is one of the very top public health leaders in the world over our lifetime."

Drawn to Africa

These days Foege, 70, is a senior fellow at the Bill & Melinda Gates Foundation.

He is a member of the scientific board that helped design and implement the Grand Challenges in Global Health initiative, funded largely by the Gates Foundation.

The initiative is exciting, he says, because it gives scientists the freedom to explore areas that traditionally haven't gotten a lot of funding. "It has the research community looking at global health," he says.

Foege is familiar with the criticisms leveled against the program, that its technology-based solutions might suck money from less sophisticated public health measures, like basic sanitation projects, and that it fails to account for the broader, cultural and economic factors that contribute to poor health.

It can only do so much, he argues. A nonprofit organization, no matter who runs it, cannot fill in for the government, which is ultimately responsible for public health – including the control of potential pandemics like avian flu.

"The Grand Challenges program is looking at the problems that poor people face that aren't being addressed by the U.N. or other agencies," he explains.

Standing 6-feet, 7-inches tall, Foege walks with long, determined strides. He walks with purpose. Around the Gates Foundation, he's known for his warmth and humor: he addresses everyone by name and asks about their families.

"It's his thoughtfulness that makes him a special leader and mentor," says Jeffrey Koplan, M.D., MPH, who succeeded Foege as CDC director in 1998 and who currently is vice president for academic health affairs at Emory University's Woodruff Health Sciences Center.

"I've met many people who are concerned about people in the abstract or as amorphous groups," Koplan says. "Bill cares about every individual he meets, but he also can see the individuals in groups and populations. He cares about those he's never met and those yet to be born."

Foege's journey to the top echelon of global health began as a boy in tiny Colville, Wash., when he first read Albert Schweitzer's autobiography, "The Primeval Forest." He felt drawn to Africa, and to medicine.

While attending medical school at the University of Washington in Seattle, Foege worked at the Seattle-King County Department of Public Health under Reimert Ravenholt, M.D., MPH.

Ravenholt, who later directed the global population program at the U.S. Agency for International Development, "quite deliberately converted me to the joys of global health," Foege says.

So did the CDC's Epidemic Intelligence Service, which Foege joined after earning his medical degree in 1961.

The service emerged from a government effort to develop a synthetic antimalarial drug during World War II. Based in Atlanta, it became the surveillance arm of the fledgling CDC, on the lookout for epidemics and outbreaks of communicable disease.

In the early 1960s, Foege, assigned to the Colorado State Health Department in Denver, got a call from a doctor on a Navajo reservation in Farmingham, N.M. "I've got a case of smallpox here," the doctor said.

Foege, who had never seen a case of the disease, pored over a medical textbook on the way to the reservation. There he found a young boy covered with a rash. None of the lesions looked like smallpox.

So Foege became the medical sleuth – knocking on doors, talking to everyone who had contact with the boy and mapping the boys' lesions every night. After a few days he had solved the mystery – the boy was recovering from measles and disseminated herpes.

House on fire

Foege's experiences with the CDC only intensified his desire to go to Africa. So, after earning a master's degree in public health from Harvard in 1965, he volunteered to serve as a doctor for a hospital operated by the Lutheran Church in Yahe, Nigeria.

In 1967, in the midst of his smallpox eradication efforts, Biafra seceded from Nigeria, prompting civil war.

His family, which by then included 1-year-old Michael, boarded an evacuation plane, leaving Foege and other doctors behind. They thought the war would end in a few days. Instead, they were drawn into a prolonged conflict: Foege saved a colleague from a Biafran soldier who was holding him at gunpoint, and he was detained several times by the rebels before he finally left the country.

He returned to Nigeria in 1968 as part of an international relief effort, and soon he was again organizing smallpox eradication. After the conflict ended in 1970, he and his colleagues were able to show that their efforts had been successful – they had quenched the disease.

In 1973, Foege moved on to India, where smallpox still raged. Within six days of starting a containment trial in four Indian states, he and his team had identified 10,000 new cases of the disease.

The health minister of Bihar Province wasn't convinced. If circle vaccination was working, why weren't the numbers going down? He wanted to reinstitute blanket vaccination.

"It was not easy to change perceptions," Foege recalls. "There was a fear that smallpox would move so fast that we would have to do mass vaccinations to keep it down – but that was not true."

For three days, he and his co-workers tried to convince the health minister to continue circle vaccination. On the day of their last meeting, desperation filled the room. If the official ordered blanket vaccination, all of their work would be lost.

Then a young Indian doctor stood up. "Mr. Minister," he said, "I'm just a village man, but when I was growing up and a house was on fire we'd put the water on that house, not the others."

Suddenly, the minister understood and agreed to give Foege one more month.

Foege (center) testifies during a Senate hearing on Legionnaires' disease held at the CDC in 1977. Joining him are CDC virologist Walter R. Dowdle, Ph.D., (left), who later served as the agency's deputy director; and David W. Fraser, M.D., a medical epidemiologist who helped identify the outbreak.

A Nigerian child, held by his mother, receives a smallpox vaccination during the 1968 World Health Organization Smallpox Eradication Project.

Members of a refugee relief team sent to eastern Nigeria during the Biafran war in 1968 include Foege (center, with pipe) and nurse practitioner Annie Voigt, CPNP, MPH (right).

Photos courtesy of the U.S. Centers for Disease Control and Prevention (CDC)

Photo of a child with smallpox taken in 1975 by Stanley Foster, M.D., a member of the CDC's Epidemic Intelligence Service, for the Global Smallpox Eradication Campaign.

“He is an extraordinarily positive person who always sees the opportunity of doing something ... He can usually see a victory and snatch it from despair.”

One month led to two months then three, and soon Foege and his team didn’t need to worry about the future of their plan. The health minister never mentioned stopping it again.

In May 1974, the number of smallpox cases had peaked; 12 months later, there were no more cases of smallpox in India. In 1979, the World Health Organization declared that smallpox had been eradicated.

“He is an extraordinarily positive person who always sees the opportunity of doing something. He is rarely pessimistic,” Koplan says. “He can usually see a victory and snatch it from despair.”

“Bill was one of the two storied heroes of smallpox eradication,” Schaffner adds. The other, Donald A. Henderson, M.D., MPH., went on to direct the World Health Organization’s smallpox eradication effort.

“There were huge successes already using strategy ‘A’ (universal vaccination),” Schaffner continues. “But for the endgame, strategy ‘B’ – the Foege strategy – was the one that worked, and he and Henderson share a claim for orchestrating the global eradication of smallpox.”

A good challenge

Foege succeeded David Sencer, M.D., MPH, as CDC director in 1977. During his tenure he broadened the agency’s international activities to deal with health crises like deadly hemorrhagic fever – Ebola – in Central Africa, and oversaw the high-profile investigation of toxic shock syndrome in the United States.

Then, in 1981, young gay men and IV drug users started dying from a rare pneumonia. By the end of 1982, even before the virus that causes AIDS was identified, Foege, Curran and their CDC colleagues had determined that the disease could be spread through blood and body secretions.

In 1984, after President Ronald Reagan appointed James Mason, M.D., as the new CDC director, Foege and several colleagues formed the Task Force for Child Survival and Development, a collaboration of the World Health Organization, UNICEF, the World Bank, the United Nations Development Program and the Rockefeller Foundation.

Foege served as executive director of the task force, which aimed for nothing less than universal immunization of children. During his six-year term, the proportion of children around the world who received basic vaccinations quadrupled – from 20 percent to almost 80 percent.

Former President Jimmy Carter later

recruited Foege to become executive director of the Carter Center and its Global 2000 program, which, among other projects, sought to eliminate "river blindness," a parasitic disease that is a major cause of blindness in Africa.

About seven years ago, Foege was teaching international health at Emory University when he was asked to advise the Gates Foundation's Global Health program.

Before taking the job, Foege drove to Plains, Ga., to talk with Jimmy and Rosalynn Carter. He had remained close to them, and he wanted to see what they thought.

"I never entertained the idea that a rich person would be interested in public health," Foege recalls. "I never thought it would be the richest man in the world or that he would be emotionally invested in public health."

He did know there was enthusiasm and energy at the Gates Foundation, and that there was real potential to transform global health. The Carters agreed.

Foege has received a sheaf of awards for his achievements: among them the World Health Organization's Health for All Medal; the Mary Woodard Lasker Award for Public Support of Medical Research and Health Sciences; and the Public Welfare Medal from the National Academy of Sciences.

Foege rarely mentions them. That's not why he did the work. That's not what inspires him.

And then there's always one more mountain to climb.

In 1997, at the age of 61 and three years after receiving a hip replacement, Foege tackled a lifelong goal, to climb 19,500-foot-tall Mount Kilimanjaro in Tanzania.

Accompanied by Paula and their three adult sons, he trudged slowly upward until – about 1,000 feet from the summit – they stopped to pitch their tents. That night as the water particles from their labored breathing formed ice crystals on the top of the tent, Paula turned to her husband. "You'd better be having a good time," she said.

Foege smiled. Of course he was having a good time.

Years later this is one of his fondest memories. Yes, it was freezing and hard to breathe, but it also was a good challenge, the kind of challenge that can truly be savored by a man who helped defeat smallpox. **LENS**

We need to view ourselves as citizens of a planet

The growing emphasis on global health is a boon not only to the developing world. It also can benefit the richest nation on Earth.

Collaborative studies in Colombia, for example, are yielding insights that may improve the care of premature infants in the United States, says Mario Rojas, M.D., assistant professor of Pediatrics at Vanderbilt University Medical Center.

In 1996, Rojas teamed up with Juan Manuel Lozano, M.D., a professor of Pediatrics and a member of the clinical epidemiology unit at Javeriana University School of Medicine in Bogotá, to form the Colombia Neonatal Research Network.

Two years later, with the help of the International Clinical Epidemiology Network and private industry, they launched their first study, a comparison of different technologies for ventilating infants with respiratory failure. It was the first randomized, controlled, multi-center trial in neonatology conducted in the country.

Colombia's infant mortality rate is about 20 deaths per 1,000 live births – three times the rate in the United States. Lack of services to support premature babies is a major reason.

Rojas and Lozano decided to evaluate high-frequency oscillatory ventilation (HFOV), an expensive technology that some studies had concluded was superior to conventional ventilation. Was it worth the investment of Colombia's already limited health care resources?

To find out, they had to ensure that ventilation was performed in precisely the same way in each of the five participating intensive care nurseries.

"They all had different protocols for management (of respiratory failure) and outcomes varied significantly between them," Rojas says. "So the great challenge was trying to get all of these medical centers and physicians to sit down together and … agree to do the same thing."

Lack of standardization also plagues multi-center trials in the United States, but Rojas, who at the time was on the faculty at the University of North Carolina at Chapel Hill, says he and Lozano weren't discouraged by the enormity of their task.

"We felt if we were able to put everything together," he says, "we would be able to do many other studies."

And so they did. Results from the four-year-long study, published last year, showed that when conventional therapy is standardized, outcomes are just as good as those obtained from HFOV. This was good news for financially-strapped countries.

Since then, the researchers have studied the use of prophylactic surfactant and nasal continuous positive airway pressure as a way to decrease the need for intubation and mechanical ventilation, and hospital-acquired infections in seriously ill newborns. They're currently seeking funding to study whether probiotics, "friendly" bacteria that colonize the gut, can prevent such infections.

These studies "may have a significant impact on health care in the United States," Rojas maintains. That's why, he says, "We need to work together …

"We need to view ourselves not only as citizens of a country … (but) as citizens of a planet."

– BILL SNYDER

A premature infant in Bogotá is fed from a cup in order to avoid dependency on an artificial nipple and to promote breastfeeding.

Courtesy of Mario Rojas, M.D.

SKIPPING THE 20th CENTURY

BY BILL SNYDER

Wireless science in resource-poor countries

Beyond the reach of power lines and paved roads in some of the most remote corners of the globe, scientific progress – and history – is being made. Researchers armed with nothing more exotic than cell phones and laptop computers are plugging into worldwide efforts to conquer ancient and modern plagues, and to prepare for those to come.

Their collaborations breach traditional barriers of geography, nation, even language, and they are transforming the way scientists are trained and science is conducted. In a sense, the digital revolution has enabled resource-poor countries to skip the 20th century, and to catapult into a new scientific age. ›››

DEAN DIXON

Dan Masys, M.D., chair of Biomedical Informatics at Vanderbilt, is heading the development of an AIDS database network in Latin America.

"In the scientific discipline of informatics, global dialogues are just a completely commonplace occurrence," says Dan Masys, M.D., who chairs the Department of Biomedical Informatics at Vanderbilt University Medical Center.

"I think that is the earmark of 21st century science," he says. "It transcends geopolitical boundaries with a transparency that is so casual and taken for granted that we don't even think about it."

Masys is the principal investigator of a five-year, $3 million grant awarded this spring by the National Institute of Allergy and Infectious Diseases to construct a database that can track the changing face of AIDS in six Latin American countries: Argentina, Brazil, Chile, Haiti, Honduras and Peru.

The grant is part of a global program called IEDEA – International Epidemiologic Databases to Evaluate AIDS – that aims to improve the monitoring of and response to the rapidly mutating human immunodeficiency virus (HIV).

"This is a very clever adversary," explains Masys, who led biomedical informatics programs at the National Library of Medicine and the University of California, San Diego, before coming to Vanderbilt last year. "Because it has a lot of genetic instability, it essentially can emerge with a resistant strain by just random selection of mutants that are not adequately suppressed by certain drugs.

"So Job No. 1 is accurate observation of patterns of disease which we can then combine with modern molecular biology and genetics to understand why those global patterns are occurring.

"This type of data can help in resource allocations in health systems planning so that each of these individual nations can anticipate patterns of disease spread or complications of HIV or the almost inevitable diffusion of new genetic variants that may have originated elsewhere in the globe ...

"And with that insight, to be able to create better drugs and intervention strategies that are not based on drugs. They may be public health strategies, sanitation or other forms of intervention that are equally or more effective."

IEDEA is not unlike the current worldwide effort to track the spread of avian flu. "That kind of early monitoring of the events that are occurring in distant countries, but which can quickly become our own health problems on a national level, is a key feature of these scientific networks that are global in scale," Masys says.

"The fundamental statement here is that knowledge is power," he asserts. "And to the extent that we have new and better means of acquiring and disseminating knowledge, we actually change the balance of power in health, the balance of power relative to our adversaries, the scourges of humanity."

Jumping into hyperspace

Masys doesn't talk like a computer nerd. That's because he's not.

Trained as an oncologist, he first realized the power of computing in the late 1970s when he wrote a software program to relieve the drudgery of tracking patients through clinical trials.

That led to an offer from the National Cancer Institute to help build a database called PDQ – Physician Data Query – "really the first electronic textbook of oncology that could be kept up-to-date over night," he says. At that point, Masys says, "I jumped to hyperspace, and have pretty much been there ever since."

After a couple of years at the NCI, he transferred to the National Library of Medicine, where – as an officer in the U.S. Public Health Service – he directed the Lister Hill National Center for Biomedical Communications.

Masys also was the program architect and first director of the National Center for Biotechnology Information, which hosts the DNA data from the Human Genome Project.

He moved to UCSD in 1994. "It was in that regard that I was first asked by the HIV centers there … to help improve their informatics and data management support for HIV research," he says. Some of their

LATIN AMERICAN AIDS DATABASE NETWORK

Team members and their countries:

ARGENTINA: Pedro Cahn, M.D., Ph.D., and his colleagues at the Huesped Foundation in Buenos Aires. The non-governmental, non-profit foundation is Argentina's best-known program for HIV prevention and care for people living with HIV/AIDS.

BRAZIL: Mauro Schechter, M.D., Ph.D., and his colleagues at the Universidade Federal do Rio de Janeiro, leaders in the field of HIV/AIDS research and care since the beginning of the Brazilian AIDS epidemic.

CHILE: Marcelo José Wolff Reyes, M.D., and his colleagues at the University of Chile School of Medicine in Santiago. Reyes directs the Arriaran Foundation in San Borja Arrairan Hospital, the nation's largest public AIDS care center for adults.

HAITI: Jean William Pape, M.D., and his colleagues at the GHESKIO Centers in Port-au-Prince, the world's oldest non-governmental organization working with HIV/AIDS care and research. GHESKIO was the first to report a case of AIDS in a developing country in 1983.

HONDURAS: Elsa Palou, M.D., head of the infectious disease service at the National Institute for Thoracic Diseases in Tegucigalpa, a national hospital that follows 1,200 patients with HIV/AIDS and which also trains health care personnel.

PERU: Eduardo Gotuzzo, M.D., professor of Medicine, Peruvian University Cayetano Heredia in Lima, director of the Alexander von Humboldt Tropical Medicine Institute, and past president of the International Society of Infectious Diseases.

Other Vanderbilt faculty members involved in the network:

Sten Vermund, M.D., Ph.D., the Amos Christie Chair in Global Health.

Richard D'Aquila, M.D., director of the Vanderbilt-Meharry Center for AIDS Research.

Catherine McGowan, M.D., director of research at the Comprehensive Care Center in Nashville, the state's largest outpatient HIV/AIDS program.

Timothy Sterling, M.D., associate professor of Medicine and an expert in tuberculosis.

Bryan Shepherd, Ph.D., assistant professor of Biostatistics.

studies were "just amazingly data intensive."

It was good training for his current challenge – achieving uniformity and consistency in a wildly diverse collection of research capabilities.

"In Haiti and in Brazil, they have very large centers with Ph.D.-level data management staff, (while) in Honduras they have one computer in a clinic, and they are paying one doctor part-time to do the data entry," Masys explains.

"So part of the aspect of this project is to provide outreach and training in the principles of what's called Good Clinical Practice, which are international standards for conducting research in a way that respects the ethical principles of informed consent and which makes the data verifiable and timely, so that it's possible to ensure scientific integrity.

"The form it will take may range from helping people to create paper forms – on three-by-five cards in some countries – and others to create secure Web portals for communication of their data. And we're prepared to do both of those things and everything in between."

The program allows for visits to each of the sites to ensure the accuracy and completeness of the data, and to provide educational outreach by Vanderbilt faculty. In return, Masys says, his co-investigators may do some teaching of their own. "This may also provide a very nice educational vehicle for Vanderbilt students to learn about how science is done in other countries," he says.

Epidemic surveillance, even one with a worldwide reach, is not new. "There have been many reporting sources," Masys says, "but they tended to report in their own format and at their own pace and using heterogeneous dissimilar computer systems …

"The difference over the last 10 years has been the emergence of the Internet and the emergence of computing technologies that are cost-effective even in developing countries, and our ability to make measurements in a systematic way across the many countries and populations of the world.

"So we can do this with greater uniformity and much faster than we could before … with eyes and ears on the ground in essentially every region of the globe."

Healthy humility

Masys is well aware of the logistical and occasional political nightmares that can play havoc with the conduct of science, but he's convinced that technology – combined with the can-do spirit displayed by

Bringing drug treatment to Vietnam

Vanderbilt psychologist Bahr Weiss, Ph.D., is helping to transform the treatment of drug addiction in Vietnam.

Still rebuilding from three decades of war, Vietnam, along with other resource-poor countries in "The Golden Triangle" of Southeast Asia, struggles with heroin addiction. Cheap, readily available and potent, heroin far surpasses marijuana as the major drug of abuse, and is the first substance most drug abusers use, even before alcohol.

Currently, there are no actual drug treatment programs in Vietnam. Drug addicts are sequestered in rural camps in the hope that ideological "re-education" and the benefits of manual labor will cure them. The relapse rate is nearly 100 percent.

"In Vietnam, people with heroin addiction are placed in what are called rehabilitation camps," says Weiss, associate professor of Psychology. "If someone denounces you as a drug addict, the local authorities give you a urine drug test. If you're positive, you're sent to a camp."

Drug addicts in Vietnam are sent to "rehabilitation camps" like this one, seen from a distance about 12 miles from the port city of Danang.

The relapse rate is, however, nearly 100 percent. Vietnamese mental health professionals are keenly aware of the limitations of this form of "treatment," Weiss says.

With pilot funding from Vanderbilt's Peabody College, Weiss and his colleagues are testing a cognitive-based treatment program in the central port city of Danang in collaboration with Trung Lam, M.D., vice director of Danang Psychiatric Hospital.

Called Self Management and Recovery Training or SMART, the program emphasizes motivation, recognition of craving and "rerouting" of negative thinking and underlying emotional issues that can perpetuate addiction.

Adapting a program developed in the United States to the tightly-knit Vietnamese family has been an interesting challenge, Weiss acknowledges.

In Vietnam, drug abuse is a source of shame for the addict's parents, siblings and even the extended family. This complicates treatment because families want to hide the individual from society, which is not realistic.

"Even for young adults of 20 or 25 years old, Vietnamese families are very involved and attempt to control their lives after they come back from the camps," he says, whereas "in the U.S., the young adults are much more likely to be on their own." Treatment in Vietnam must be adapted to consider the family.

Residents of a drug rehabilitation camp outside Danang play volleyball in an outdoor courtyard.

Photos courtesy of Bahr Weiss, Ph.D.

"Collaborating with Dr. Trung and his colleagues has been a real honor and pleasure," Weiss notes. "He is one of the smartest, most open-minded, hardworking and selfless people I have ever met, either in the U.S. or Vietnam."

If SMART proves to be effective in Vietnam, Weiss hopes the Vietnamese government will fund the program and that it will be adopted by mental health care providers. The research also may yield useful information for treating addiction among Southeast Asian immigrants to the United States, he adds.

– COLLEEN CREAMER

his co-investigators – will overcome any challenge.

"You have science that runs on batteries in many developing nations of the world," he explains. "Combine that with innovations such as Wi-max, a wide-area data networking, where one can put a transmitter on a single cell-phone tower and be able to provide high-speed Internet services to a region that's 30 miles in diameter from one device.

"That is the kind of leap forward that means we don't need wires to connect with one another either by voice or data across increasingly large regions. The net effect of that is being able to recruit new people into research activities who were not previously involved because of the cost and expense of installing an infrastructure for doing that."

Even if funding for the network doesn't continue beyond five years, the relationships forged by this project will probably be "enduring legacies," Masys predicts.

"The international bonds of trust and collegiality and friendship that come out of these research collaborations are likely to be the foundation for other abilities we'll have in the future to push the boundaries of science … and (they won't be) limited to HIV."

The Internet can be a humbling experience for U.S. researchers, who are accustomed to being at the pinnacle of scientific achievement.

"That sensitivity of knowing instantly how other people interpret what we're doing is a very important component of good citizenship in a global knowledge economy," he says, "and I think also a healthy form of humility.

"National chauvinism doesn't really suit us very well in a world where what we do dramatically affects others, and what they do dramatically affects us on an hour-to-hour basis.

"… So this shrinking globe, propelled by competing communications technologies, is probably the single greatest force at work I think in our society," Masys concludes. "It's done more to transform the nature of business and the nature of government and the nature of political forces than anything that has preceded it.

"It's rightly viewed as a tremendous threat to totalitarian regimes, where controlling the flow of ideas is essential to maintaining one's power base.

"It's funny," he wonders, "if we had the Internet somehow magically appearing in antiquity, would we have even invented countries?" **LENS**

Aiding the most vulnerable

Ward for women patients in Sassoon General Hospital, Pune, India. Courtesy of Vikrant Sahasrabuddhe

This spring Vikrant Sahasrabuddhe, M.D., MPH, DrPH, returned to Pune, India, to help some of the most vulnerable members of the Indian society – HIV-infected women.

Sahasrabuddhe, a research assistant professor of Pediatrics at Vanderbilt, is directing a study aimed at testing a visual inspection method to screen for cervical cancer, the leading cause of cancer deaths among Indian women.

The risk of cancer is particularly high among women who are infected with HIV.

In the United States, the Pap smear is credited with reducing the cervical cancer death rate by 70 percent since it was introduced in the early 1940s.

In resource-poor countries like India, however, collecting smears of cervical cells, sending them to the lab for analysis, then reporting the results is "a recipe for failure at multiple stages," says Sahasrabuddhe who earned his medical degree from the University of Pune. "Most women do not even get a once-in-a-lifetime Pap smear exam."

An alternative is visual inspection with acetic acid (VIA), a one-step clinical test that can be performed by a nurse and which may be as accurate as the Pap smear. The cervix is viewed through a speculum after application of acetic acid. "If the cervix turns white, it's an indicator of a precancerous lesion," he says.

While earning his doctorate in Public Health at the University of Alabama at Birmingham (UAB), Sahasrabuddhe co-directed a pilot study of VIA in HIV-infected women in Zambia under the mentorship of Sten Vermund, M.D., Ph.D.

Based on encouraging early results, the study is being expanded to all of the public health clinics in Lusaka, the Zambian capital, and to Pune, a city of 3.5 million people southeast of Mumbai (formerly Bombay). "It's right on the Mumbai-Chennai highway, which is a hotbed of HIV transmission within the south of India," Sahasrabuddhe says.

Vermund, who joined the Vanderbilt faculty last year, is the study's principal investigator, and Sanjay Mehendale, M.D., MPH, senior deputy director of the National AIDS Research Institute in Pune, is the principal collaborator in India. The study will recruit patients at the Sassoon General Hospital, the teaching hospital of B.J. Medical College in Pune.

Other partners include UAB and John Hopkins University, which has been involved with multiple HIV/AIDS research collaborations in Pune. In addition, two Vanderbilt students will contribute to the research this summer.

"The diversity of the human population in India is going to open a lot of doors for people who are interested in studying medicine and health," Sahasrabuddhe explains. The study also provides insight into the problem of health care disparities, no matter where in the world they occur.

"We're looking at socioeconomic barriers, human factors, institutional or systemic factors which prevent access to screening," he says. Interventions that don't account for these factors "are bound to fail."

– BILL SNYDER

Our work is hardly done

BY BILL SNYDER

In late 2001, a team of U.S. and Zambian investigators launched an ambitious program to prevent HIV-positive women from infecting their babies.

Within two years, HIV counseling and testing was being provided in public delivery clinics throughout the Zambian capital, Lusaka.

Thousands of HIV-infected pregnant women were given tablets of nevirapine, a drug that can dramatically reduce mother-to-child transmission of the virus when taken by the woman during delivery, and when given soon after birth to the baby.

Yet when the researchers examined the results of their labors, they had an unfortunate surprise: only 30 percent of the women had actually taken their pills.

"We were disappointed, but had the critical information to improve our program," says Sten Vermund, M.D., Ph.D., who now directs the Institute for Global Health at Vanderbilt University School of Medicine. "It's not so easy to implement a large program in some of the world's poorest countries, even with the advantage of free drugs and relatively straightforward interventions."

At the time, Vermund was director of the Sparkman Center for Global Health and director of the Division of Geographic Medicine at the University of Alabama at Birmingham (UAB).

A former chief of the AIDS Vaccine Trials and Epidemiology Branch at the National Institute of Allergy and Infectious Diseases (NIAID), he had studied the spread and treatment of HIV and other sexually transmitted diseases (STDs) all over the world.

In 2000, Vermund and Moses Sinkala, M.D., with fellow UAB faculty members Jeffrey Stringer, M.D., and Robert Goldenberg, M.D., founded the Centre for Infectious Disease Research in Zambia (CIDRZ) to facilitate AIDS research in collaboration with Zambian public health officials led by Sinkala.

The effort was supported initially by a training grant from the Fogarty International Center of the National Institutes of Health and by research funding from the Elizabeth Glaser Pediatric AIDS Foundation. Later, CIDRZ became a clinical trials research unit of the HIV Prevention Trials Network, supported by NIAID.

CIDRZ also received a $4 million grant from the Bill & Melinda Gates Foundation to set up a paperless reference system in the clinics.

Yet technology was not enough. When the researchers examined what had gone wrong, they found gaps at every step along the "prevention cascade" to prevent HIV transmission from mothers to their infants.

In some cases, pregnant women weren't offered nevirapine during their clinic visit. Or they forgot to take the drug when they went into labor. Or they gave their pill to a sick relative.

By attending to each step, the researchers have managed to increase nevirapine coverage to nearly 60 percent. "Still, over 40 percent of women are falling through the cracks," Vermund says. "So our work is hardly done."

With support from several U.S. and international aid agencies, and especially the $20 million in grants received in 2004 from the President's Emergency Plan for AIDS Relief (PEPFAR), the Zambian program has been able to dramatically extend its reach.

Stringer and Isaac Zulu, M.D., of the University Teaching Hospital in Lusaka, are the co-principal investigators for the grants.

"PEPFAR has transformed our operation in Zambia," Vermund says. "We have got over 17,000 persons on ART (anti-retroviral therapy) in the past two years, and we have over 30,000 people in care. That was done because we got the money."

This winter Vermund turned his attention to Mozambique which, like its neighbors, has a numbingly high rate of AIDS.

The Vanderbilt-led effort, which has just garnered a PEPFAR grant, will initiate ART and HIV care in three small towns in rural Zambézia Province. Team members include:

Maria de Fatima Lima, Ph.D., Dean, and Christine Minja-Trupin, Ph.D., School of Graduate Studies and Research, Meharry Medical College, Nashville;

J. Gary Linn, Ph.D., professor of Nursing in the Center for Health Research, Tennessee State University, Nashville;

Paula Schuman, M.D., MPH, director of the HIV/AIDS Center at Virginia Commonwealth University, Richmond;

Mauro Schechter, M.D., Ph.D., professor and director of AIDS Programs at the Universidade Federal do Rio de Janeiro; and Adele Schwartz Benzaken, M.D., of the Alfredo da Matta Foundation in Manaus, Brazil.

Brazil shares Mozambique's national language – Portuguese.

The program won't just be about AIDS. "You cannot provide HIV care without broad-based upgrading of the primary health system," Vermund says. "HIV care settings with excellent laboratories don't make sense if the adjacent clinic is bereft of water, sanitation and electricity …

A gravel maker and his wife use hammers to crush stone near Lusaka, the Zambian capital.

Photo courtesy of Sten Vermund, M.D., Ph.D.

"So we're going be in there with HIV and TB and STDs, and primary health care and vaccinations and upgrading of maternity services and chronic care services for kids."

PEPFAR won't pay for that kind of broad-based infrastructure development. Nor does it cover research to determine the most cost-effective way to provide AIDS care and treatment.

According to a recent Government Accounting Office report, its emphasis on abstinence-until-marriage programs has made it difficult for countries to "respond to local needs, local epidemiology and distinctive social and cultural patterns." An Institute of Medicine evaluation of the program's effectiveness is under way.

Still, Vermund argues, "it's the best thing the Bush administration has done … It's remarkable how well it's working." LENS

Q & A

INVESTING SOCIAL CAPITAL

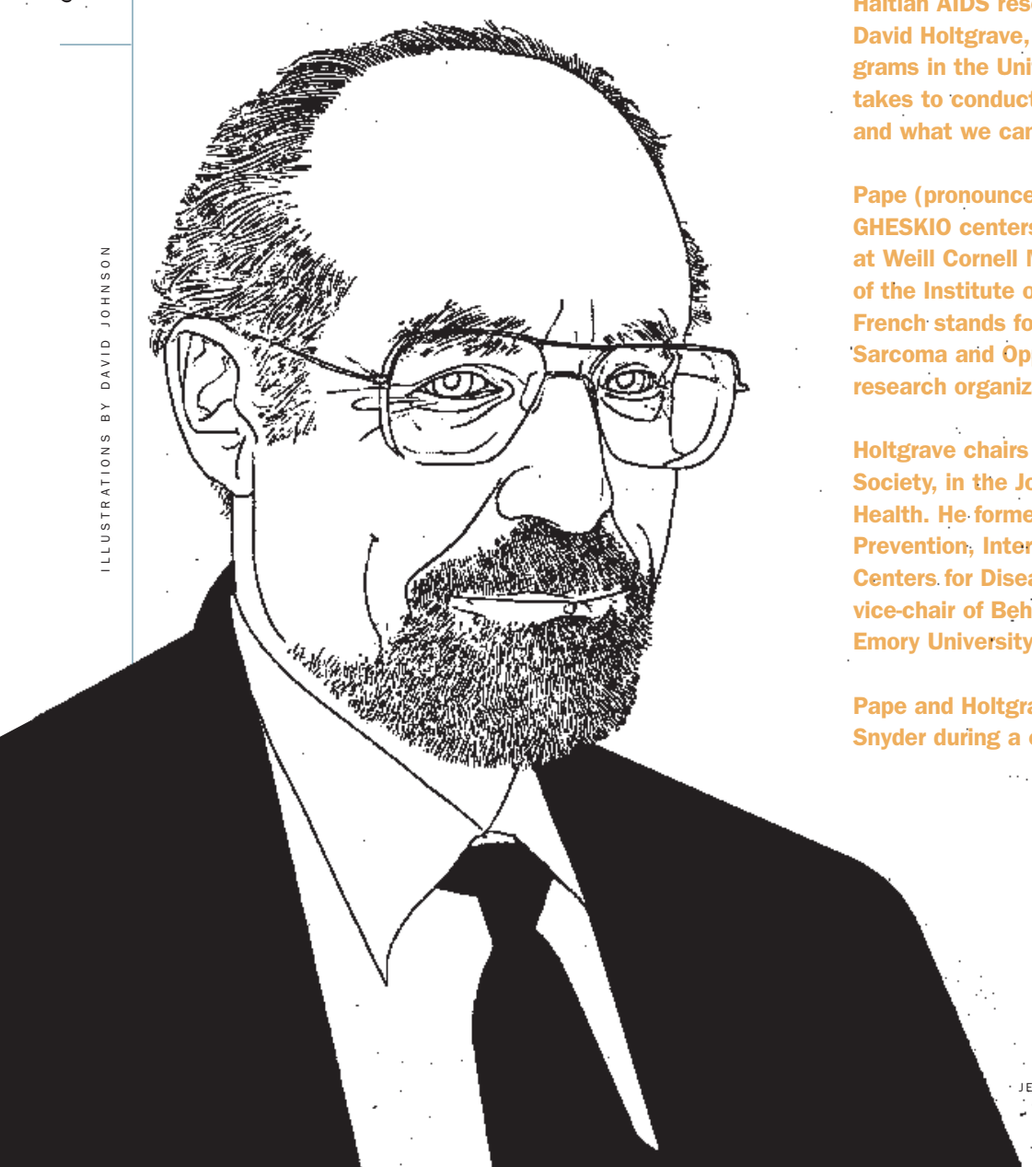
Keys to conducting research abroad ... and at home

Haitian AIDS researcher Jean William Pape, M.D., and David Holtgrave, Ph.D., an expert on HIV prevention programs in the United States, share their views about what it takes to conduct AIDS research in resource-poor countries, and what we can learn from these experiences.

Pape (pronounced "Pop") is founder and director of the GHESKIO centers in Port-au-Prince, professor of medicine at Weill Cornell Medical College in New York and a member of the Institute of Medicine. GHESKIO, an acronym that in French stands for the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections, is the oldest AIDS research organization in the developing world.

Holtgrave chairs the Department of Health, Behavior and Society, in the Johns Hopkins Bloomberg School of Public Health. He formerly directed the Division of HIV/AIDS Prevention, Intervention Research and Support at the U.S. Centers for Disease Control and Prevention (CDC), and was vice-chair of Behavioral Sciences and Health Education at Emory University's Rollins School of Public Health.

Pape and Holtgrave were interviewed by *Lens* editor Bill Snyder during a conference call in January 2006.



ILLUSTRATIONS BY DAVID JOHNSON

JEAN WILLIAM PAPE, M.D.

Dr. Pape, I'd first like to discuss the paper, "Anti-retroviral therapy in 1,000 patients with AIDS in Haiti," published last December in the *New England Journal of Medicine*. What were some of the logistical, economic and social barriers to conducting this research?

The major difficulties that we encountered were mostly related to adherence. It is very difficult to have anybody stay on medication for a long time; it's even more difficult for people who are very poor or cannot afford the costs of transportation and could not afford to eat on a daily basis.

This is why we developed a team approach involving the psychologist or social worker, the nurse, the pharmacist, the physician – actually the physician was the least important – as well as people living with AIDS on HAART (highly active anti-retroviral therapy) who also worked with us.

We also had a very sophisticated data management system to keep track of patients' visits. This system informs immediately the staff about those who missed an appointment. Since patients do not have telephone at home, we had to train field workers to visit them at their home, report on their status and give them another appointment. We also had to provide nutritional support and provide as well free transportation to and from the clinic … With this package the adherence issues were mostly resolved.

In addition, this study was conducted at a very difficult time. President Aristide was sent into exile and there was a lot of disruption of the social matrix of this country. There was a lot social unrest. There was a lot of political violence. And we had to develop contingency plans.

Fortunately, we live in Haiti. We know that this is something that can occur, and we have developed contingency plans and were able to place medications at various sites in the city, and give phone cards to our patients so that they could call us and know where to go and get their drugs … And this way all of our patients stayed on their medication even during this chaotic period.

What is important for researchers from the United States to consider when conducting studies in resource-poor countries?

I can list 10 very important points. The first one is that the research has to be focused.

It needs to be cooperative with clear advantages for both parties; you cannot just conduct research in a country and not involve a local entity.

The parties involved must be credible. In some cases it could be the reputation of one person that will decide on the fate of the research.

You have to plan long term. It may take 15 to 20 years. This is what it takes for capacity building in human resources, equipment and infrastructure so that when the research is done, there is something left in the country.

It is necessary to share and use the results of the research in the country where it is conducted.

It has to be comprehensive. You should have a holistic approach involving patient care and training whenever possible. We have been focused on the family unit. This has been our strength here at GHESKIO.

The research should be relevant. It should address important public health issues faced by the country where the work is planned.

It must rest on strong ethical standards.

In addition to that, you need to have a research where you have collaboration with the government whenever possible, but in a manner that is apolitical.

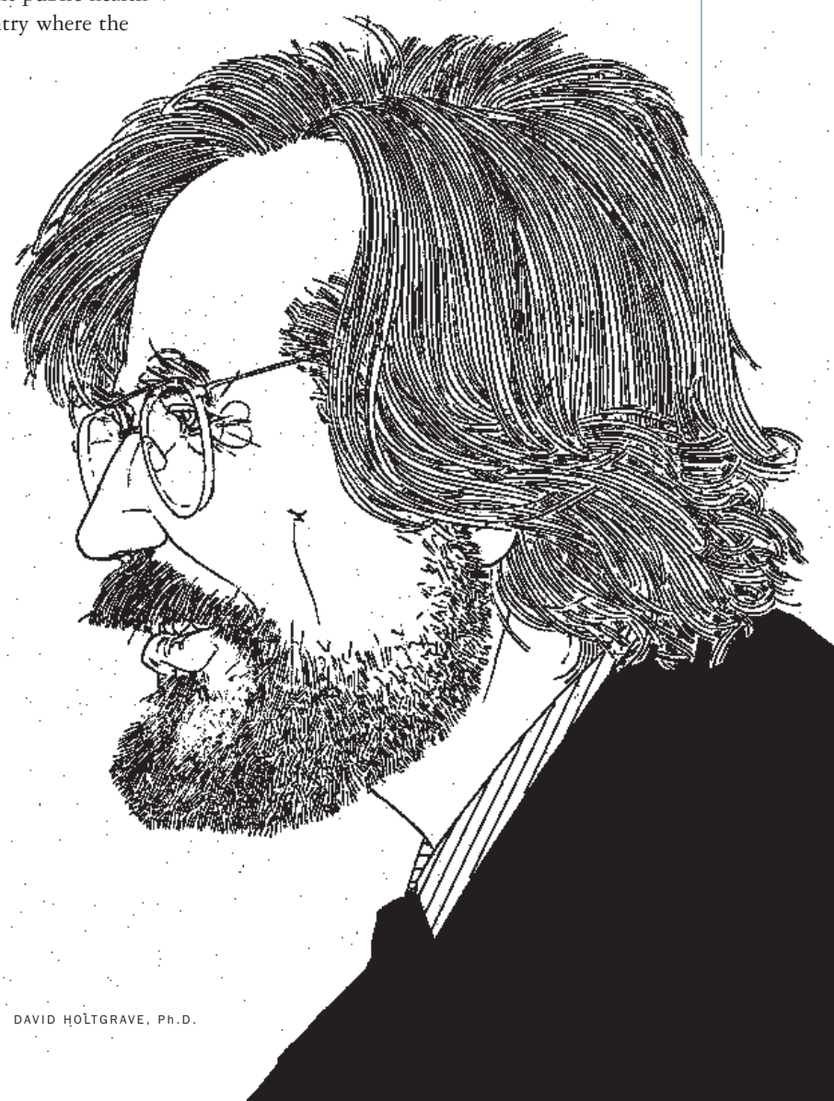
And finally, you need community support.

Dr. Holtgrave, you have spoken recently about why the CDC was unable to achieve its goal last year of halving the annual number of new HIV infections. Can you elaborate?

In the U.S., prevention programs seem to have made a difference in terms of bringing infections down to 40,000 infections a year from a peak of about 160,000 infections a year in the mid-1980s. That drop is an important measure of prevention success.

We think that over the course of the epidemic, several hundred thousand infections have been prevented in the U.S.; perhaps as much as a little over a million.

I think the question that you're raising is a very important one for the U.S. at the moment. CDC set a goal of reducing new infections by half by 2005, from 40,000 a year down to 20,000 a year.



DAVID HOLTGRAVE, Ph.D.

Clearly 2005 is over, and CDC's continued best estimate of the number of new infections a year is (still) 40,000.

One important reason is resources. There have been at least two published estimates of how much additional resource would have to be made available for a person at risk of infection or transmission in the U.S. to receive good quality prevention services.

The best estimate is about $300 million a year. That would mean that CDC's budget would have to go from about $700 million to about $1 billion per year.

However, over the last few years, if you adjust for inflation, the investment in prevention in the U.S. is either staying the same or actually going down a little bit. And so unless we expand our efforts to try and address these unmet needs, we're going to fall short. I am hoping that the $93 million increase for domestic HIV prevention in the president's fiscal year 2007 budget proposal is one step in a better direction.

Another very important issue is having science-based prevention tools that we know make a difference, yet seeing those interventions sit on the shelf – not be able to be used.

Take needle and syringe exchange programs. A lot of scientific studies show that they do seem to make a difference in terms of reducing needle sharing and reducing HIV infections. They have even been found to be cost-effective. But there continues to be the ban on use of federal money for needle and syringe exchange programs.

Some states, cities and private funders have started to make up some of that difference, but still the federal ban is an important barrier.

The third major area, discrimination and stigma, is also very important to address in this society. If populations who are disproportionately impacted with HIV are discriminated against or stigmatized, it's very hard to put in place effective prevention services.

Dr. Pape, are you seeing these kinds of barriers also in Haiti?

We have the same (problems) but with much greater magnitude. Haiti has a lot of the problems that facilitate HIV transmission.

We started with a very high HIV seroprevalence; we have the highest HIV seroprevalence outside of Africa. We are the poorest country in the Caribbean, (and have) high rates of sexually transmitted diseases, which are known to be co-factors for HIV transmission.

We have what I would call sexual promiscuity, because men have contact with many women and have contact with commercial sex workers. At one point in 1982, 62 percent of sex workers were HIV infected.

We have a high illiteracy rate – about 40 percent. But still at the time when we had very little resources, with prevention in particular, we've been able to reduce the seroprevalence rates in documented national surveys from 6.2 percent in 1993 to 3.1 percent in 2003.

They're going to have another (survey) this year, and I expect that (the rate) will be lower than 3 percent.

What can the United States learn from research conducted in the developing world?

Number one, it is possible to conduct high-standard research with high ethical values in developing countries.

With limited resources you can obtain excellent results – if you have a well-conceived plan.

And the third thing which we have done is that if you can rapidly implement the results of the research, (it) will have national impact.

Dr. Holtgrave?

The 100-percent condom use program that was put in place in Thailand, I think, suggested a very interesting and effective kind of policy. Programs for injection drug users early in the epidemic seemed to make a major difference in Australia.

The idea of couples counseling (for HIV prevention) has been an important one now throughout the epidemic. That work was really pioneered in Africa.

And so I believe there are many lessons to be learned from around the world about what kinds of policies are most effective.

Dr. Holtgrave, your department at Johns Hopkins is exploring how multi-level interventions work together to improve health. Why is this approach important?

The new Department of Health, Behavior and Society will look at a number of different disease areas, from HIV to cancer to cardiovascular disease to diabetes.

When we consider any one of those specific disease areas, we don't think about what's the one magic bullet to change health behavior in that particular area … but rather, we try to understand how to intervene at all or at least a multiple of those levels.

What are those levels? Well, you might intervene with one individual at a time, with a couple, a family, with the community, with the whole society or a whole nation, and you might even go beyond that and say you want to change policies, laws or even the environment in that nation.

In HIV prevention, our department is interested in individual counseling, group and community-level interventions, services that address entire social networks, and structural interventions such as using housing for homeless persons as a kind of HIV prevention intervention. Further, we are interested in addressing multiple levels at once.

Dr. Pape, how important have been the contributions of your colleagues at Cornell and Vanderbilt?

They've been invaluable. There is no way that we could have done what has been done, and there is no way the epidemic could be somewhat controlled in Haiti without that kind of support.

With Vanderbilt, what has been very important is the contribution of Peter Wright, M.D., who heads pediatric infectious diseases at Vanderbilt, in getting (GHESKIO) into (testing) HIV vaccines.

Vanderbilt and Cornell have been instrumental to initiate ACTG (AIDS Clinical Trial Group) studies. Those were very, very important studies for us to initiate and scale-up HAART in Haiti, as our staff learned from the vigorous research training and applied the experience acquired to patient care. We could not have enrolled 100 new patients per month, and that's the rate we've been scaling up HAART. We have now over 3,000 patients on HAART.

We also had equipment that was necessary to do the tests and the reagents, as well as specific clinical research projects, where you could train a young faculty staff member in the conduct of research. They are the ones who said, 'Why can't we apply these same research tools for patient care?'

I think that separating completely research from patient care doesn't make a lot of sense because research has been instrumental in both training the personnel, because we train them with the results of the research that we conduct on site, and also it has been instrumental to provide the proper care.

What is the most important kind of international support that should continue for your program?

At present because we have very well trained staff, I think the provision of the drugs is essential, as well as the reagents, because the one-year cost for placing a patient on HAART in Haiti is still expensive – around $2,000 a year per patient.

Dr. Pape, are we training enough researchers to do the studies that need to be done on a global scale?

Clearly, in Haiti, we are not training enough people.

We've trained since 1992 over 10,000 health personnel including 2,000 physicians. Unfortunately many of those physicians tend to leave Haiti. We've lost over half of them, but we've also trained psychologists and trained social workers.

Now what I think is important in a place like Haiti is providing on-the-job training. Training them behind a blackboard is not going to make a difference. We give them very little theoretical training. The majority of the training is done on the job.

What AIDS has done also is created teamwork. It's not a team composed only of physicians. We also have people living with AIDS who are part of that team, field workers.

Field workers are our extension because people here don't have phone numbers, so even the best address would not get you close to their home. You need field workers who are able to visit patients at their homes and verify that their address is correct.

Dr. Holtgrave?

Previously I think there was a sense in public health that we needed to bring people together from a lot of different disciplines. But now increasingly there's recognition that as we train people in graduate programs and even now in undergraduate programs in public health, it's important to give people a broad array of skill sets.

A special skill in and of itself is how to work together on an interdisciplinary team and how to be appreciative of other disciplines, how to phrase questions in a way to draw out the views of people from other disciplines. More and more we're seeing people trained to be multidisciplinary themselves as opposed to simply bringing one disciplinary viewpoint to a multidisciplinary team.

That doesn't mean that you wouldn't still have teams that included people from a variety of different fields, but it's important to have people who've been trained in how to work in an interdisciplinary way and who themselves have experienced some training in all of the different areas of public health.

One of the things we've been interested in studying is the importance of not only poverty and income inequality as predictors of infectious diseases, but also social capital as well, and looking at how strongly people are tied together in a community.

Do people say that they have friends in the community? Do they share meals together? Do people belong to social organizations together? Are these social factors promoters of – or protective against – infectious disease?

With regard to predictors of STDs and HIV/AIDS and even teen pregnancy, we're finding that although poverty, income inequality and social capital are all important, actually it is social capital that seems to be the strongest predictor.

We have found that in states where there is higher social capital (higher interconnectedness), there are actually substantially lower STD and AIDS case rates. Teen pregnancy is also much lower when social capital is high. Social capital is protective.

That suggests that maybe if we were able to build stronger neighborhoods, stronger communities, that we might be able to intervene in multiple diseases at one time.

Dr. Pape, have you looked at the element of social capital in Port-au-Prince?

Yes we have. We work with a very poor community, and most of them live in the slums. And what we have seen is that very often a very small amount of (social) capital makes a huge difference in both education and health behavior and diseases. **LENS**

An ethical dilemma

Vulnerability.

It's at the core of ethical issues related to research with indigenous populations, says Ellen Wright Clayton, M.D., J.D., the Rosalind E. Franklin Professor of Genetics and Health Policy at Vanderbilt University.

"There are concerns that indigenous and isolated populations are being involved in research that may not ultimately be of benefit to them, that may go counter to their world view, that they may not understand," she says. "There are any number of ways in which research with these populations becomes problematic."

Clayton is leading a work group that aims to catalyze the development and adoption of a set of comprehensive ethical guidelines for researchers to use when studying indigenous or isolated populations. The group is unique in its composition, Clayton says. Anthropologists, political scientists, biomedical researchers, ethicists, and theologians are coming together to consider the issues.

"It's important to really understand the full breadth of the problem, in all of its complexity and from a variety of different disciplinary perspectives, before we can even begin to come up with solutions that may be helpful," Clayton says.

"We have to realize that we have a particular scientific world view of causation that may not be shared with indigenous populations," she adds.

"We all have some degree of ethnocentric views," says Mario A. Rojas, M.D., assistant professor of Pediatrics at Vanderbilt. "We have to check ourselves … in order to be able to sit down with people from other communities and different cultures, and work together to solve specific problems."

That 'sitting down and working together' is essential, Clayton agrees. "We must engage with the indigenous groups and create partnerships that leave them at the end of the day not feeling like they've been taken advantage of," she says.

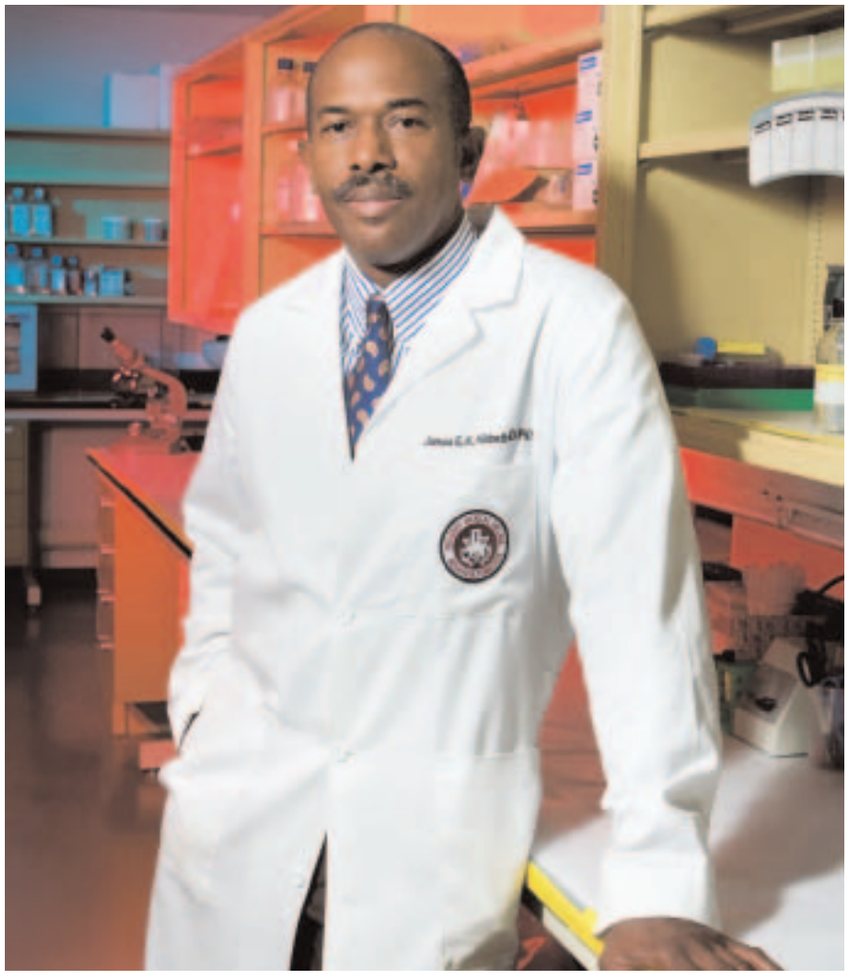
"We have to be serious in thinking about what they're going to get back. It may be a pharmaceutical that's developed, a certain amount of the profits, or research and health care capacity. If you're going to involve indigenous populations in research, then you have to confer some benefit to them."

Partnerships and community engagement can be tricky to negotiate, cautions Clayton.

"Are you working with the right people in the group? Are those leaders keeping the interests of the group in mind? How do you think about informed consent in a hierarchical society? How do you think about research in a population that doesn't give women an independent say?

"We have clear norms in the United States that don't always overlay neatly on local norms," she says. "We're currently in the debate about these issues."

– LEIGH MACMILLAN



James Hildreth, M.D., Ph.D., wants to empower women to protect themselves from AIDS.

Meharry Medical College

Acts of grace

By Bill Snyder

This summer James Hildreth, M.D., Ph.D., will meet with Zambian officials to discuss ways to partner in the first clinical trials of a "chemical condom" that could protect women from HIV infection.

"If you're a woman in a third-world country, and you cannot negotiate the use of a condom by your male partner … you're always at risk," says Hildreth, who just finished his first year as founding director of the Meharry Medical College's Comprehensive Center for Health Disparities Research in HIV.

A microbicide-containing vaginal cream could "empower women to protect themselves," he says.

Hildreth started investigating HIV as a young faculty member at Johns Hopkins University in the late 1980s, but his determination to solve problems that disproportionately affect poor people and minorities was forged 20 years earlier, in segregated small-town Arkansas.

When he was 11, he lost his father to cancer. "Because we were poor and because we were black, my father received little care," he says. "It made me a very angry young man."

Months later, his hero, the Rev. Martin Luther King Jr., was cut down by an assassin's bullet. "My despair gave way to rage. I turned completely inward and didn't speak to anybody."

Fortunately his "praying, patient and insightful" mother Lucy helped him to channel his anger in ways that nourished rather than destroyed him.

"Dr. King faced unimaginable hatred and enmity … and yet he never responded in kind," Hildreth told Vanderbilt medical and nursing students during a lecture this winter honoring the civil rights leader. "My mother helped me understand there was no reason to hate ... If I was to be true to Dr. King, I had to have the same grace he had."

Hildreth went on to Harvard, won a Rhodes scholarship to Oxford where he earned a Ph.D. in immunology, and received his medical degree from Johns Hopkins.

At first he wanted to become a transplant surgeon, but soon turned his attention to HIV after witnessing the disproportional impact of AIDS on "the poor, the disadvantaged and people of color."

Applying his expertise in cellular immunology, he and his first graduate student, Rimas Orentas, reported in 1989 that HIV essentially "hijacked" proteins on the surface of certain white blood cells in order to attach to and infect the cells. The points of attachment are called lipid "rafts" because they are full of cholesterol.

Hildreth and his colleagues wondered what would happen if they disrupted these viral "lifeboats." By 2001, they had an answer: when cholesterol was "sucked out" of the membrane by a lipid-attracting chemical called beta-cyclodextrin (BCD), HIV was no longer able to infect its target cell.

Within three years, Hildreth and his colleagues had developed a BCD-based cream that, in animal studies, blocks HIV infection.

About that time, he received an offer to direct a new AIDS research center at Nashville's historically black medical college. He declined twice. His wife, Phyllis, urged him to reconsider.

"As I thought about it … to do (my work) at this place, which has been battling health disparities since its inception, became more and more appealing," Hildreth recalls. "It would be a tremendously powerful thing if even a partial solution to the AIDS problem could have its birth here at Meharry … I felt compelled to come."

In concluding his lecture to the Vanderbilt students, Hildreth returned to the grace that illuminated King's life.

"This is your world to take and do with as you please," he said. "But … I beg you not to become what Shakespeare calls the indifferent children of the world, who would stand and watch as the world falls into chaos … The bottom line is there is a lot of work for us with grace to do." LENS

For more information …

Links to programs mentioned in this issue, and others that are involved in efforts to improve global health.

From "One bucket at a time" – page 4
Lwala Clinic Project
www.mc.vanderbilt.edu/lwala

Vanderbilt Office of Active Citizenship and Service
Global Service Opportunities
www.vanderbilt.edu/oacs/global

United Nations Millennium Project
www.unmillenniumproject.org

From "Tricking the mosquito's nose" – page 10
Grand Challenges in Global Health
www.gcgh.org

More on malaria mosquito research
www.vanderbilt.edu/exploration/stories/gcgh.html

From "Thwarting a clever devil" – page 15
Aeras Global TB Vaccine Foundation
www.aeras.org

From "Another mountain to climb" – page 16
U.S. Centers for Disease Control and Prevention (CDC)
Coordinating Office for Global Health
www.cdc.gov/cogh

Bill & Melinda Gates Foundation
Global Health program
www.gatesfoundation.org/GlobalHealth

The Carter Center Health Programs
www.cartercenter.org/healthprograms/healthpgm.htm

From "Skipping the 20th century" – page 22
The Caribbean, Central and South America network for HIV epidemiology (CCASAnet)
http://ccasanet.vanderbilt.edu

From "Aiding the most vulnerable" – page 25
National AIDS Research Institute, Pune, India
www.nari-icmr.res.in

From "Our work is hardly done" – page 26
Centre for Infectious Disease Research in Zambia
www.cidrz.org

President's Emergency Plan for AIDS Relief
www.pepfarnpi.com

From "Investing social capital" – page 28
GHESKIO: Haitian Study Group on
Kaposi's Sarcoma and Opportunistic Infections
www.haitimedical.com/gheskio

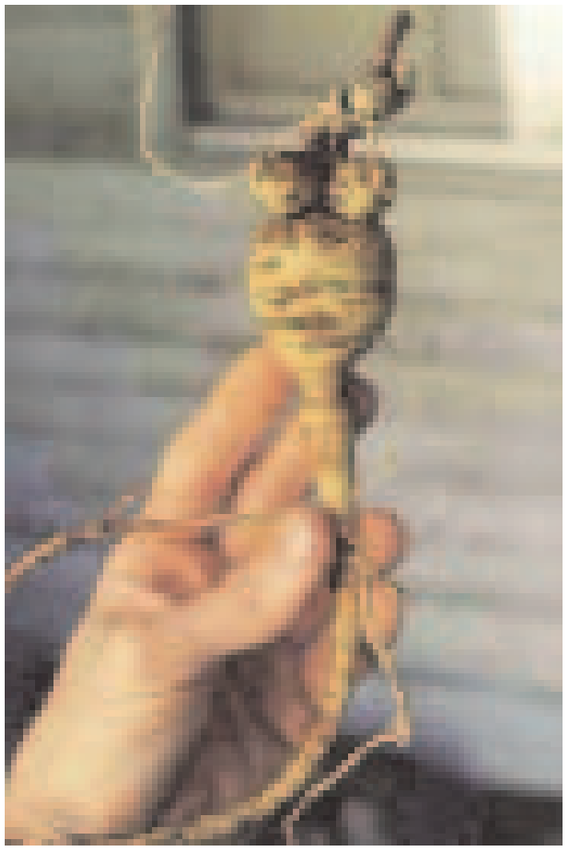
Johns Hopkins Bloomberg School of Public Health
Department of Health, Behavior and Society
www.jhsph.edu/dept/hbs

Related sites
The Global Fund to Fight AIDS, Tuberculosis and Malaria
www.theglobalfund.org/en/

William J. Clinton Foundation HIV/AIDS Initiative
www.clintonfoundation.org

A large epidemiological study conducted in China by Vanderbilt researchers suggests that ginseng, one of the most widely used herbs in traditional Chinese medicine, may improve survival and quality of life after a diagnosis of breast cancer.

Photo courtesy of Scott Harris, Sylvan Botanicals



IN THE NEXT ISSUE:

The science of large numbers
Cohort studies involving thousands of people are revealing links between diet and cancer.

Reading the genome
Scientists hope that the secrets of tumors can be divulged from their unique DNA sequences.

How cancer starts
Signaling pathways involved in normal tissue growth may be crucial to understanding cancer.

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