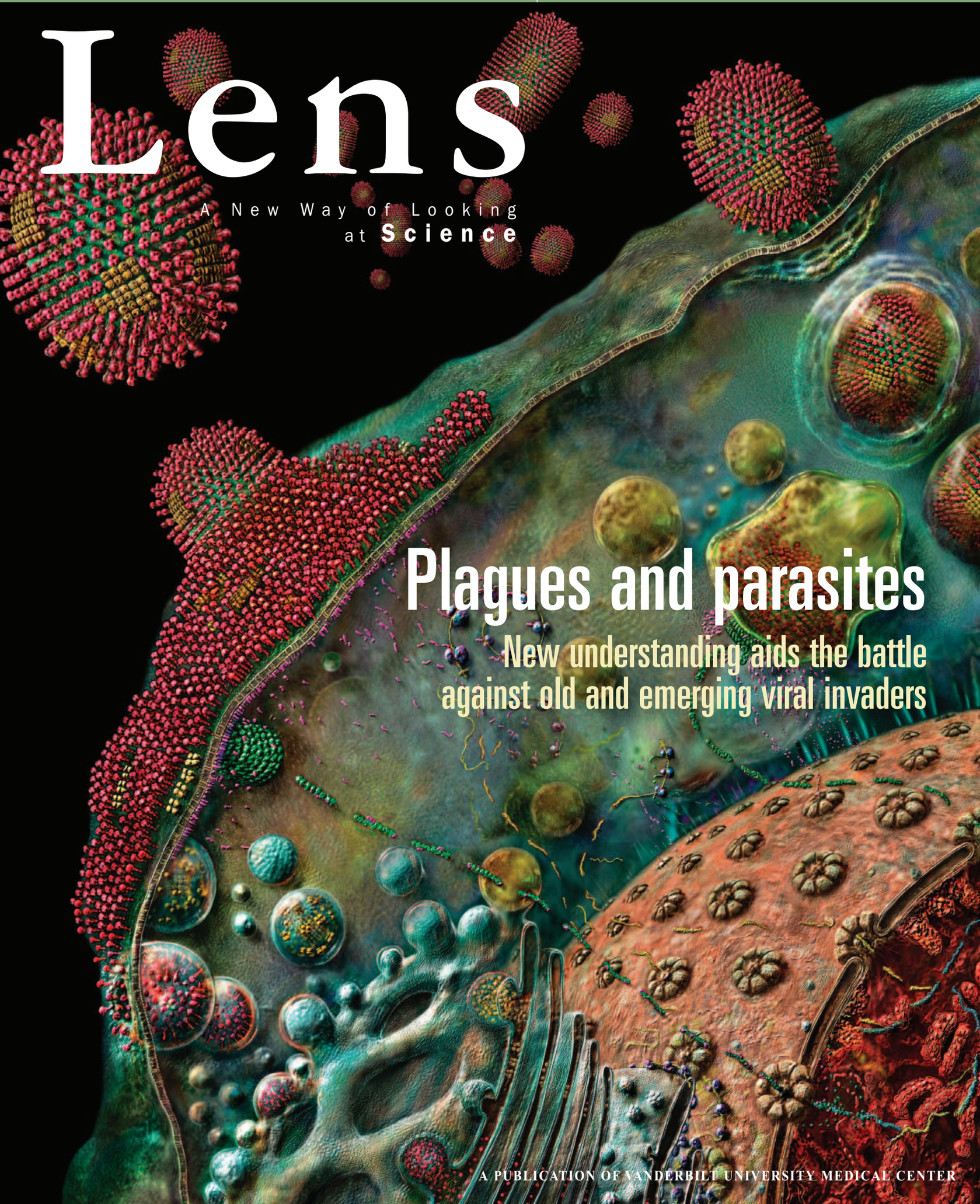
SPRING 04

Lens

A New Way of Looking at **Science**



Plagues and parasites

New understanding aids the battle against old and emerging viral invaders

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

SPRING 2004

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You see things; and you say "Why?" But I dream things that never were; and I say "Why not?"

– GEORGE BERNARD SHAW

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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 a greater appreciation of the technological, economic, political and social forces that guide it.

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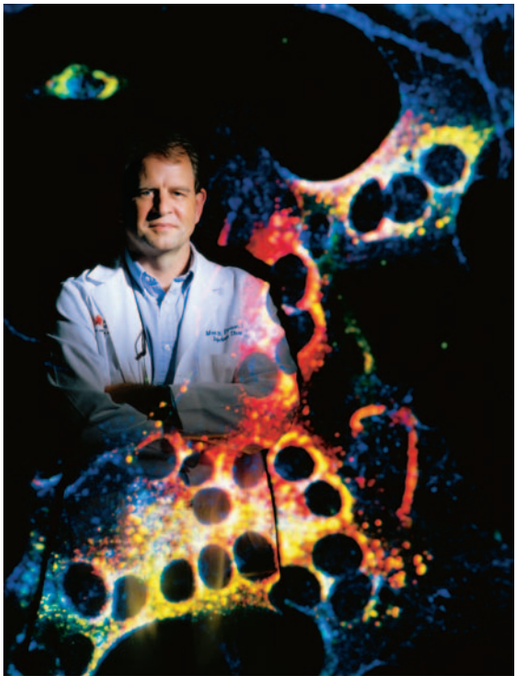

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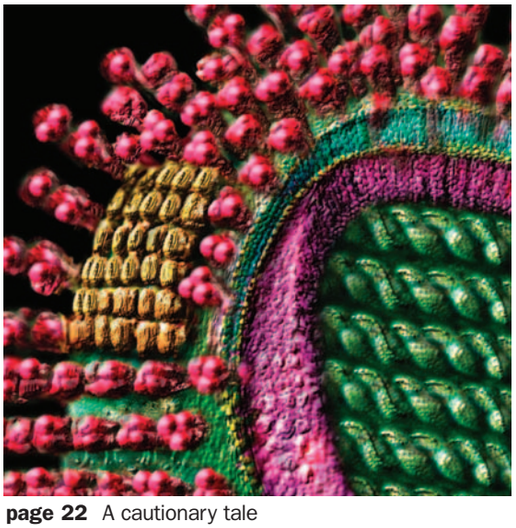

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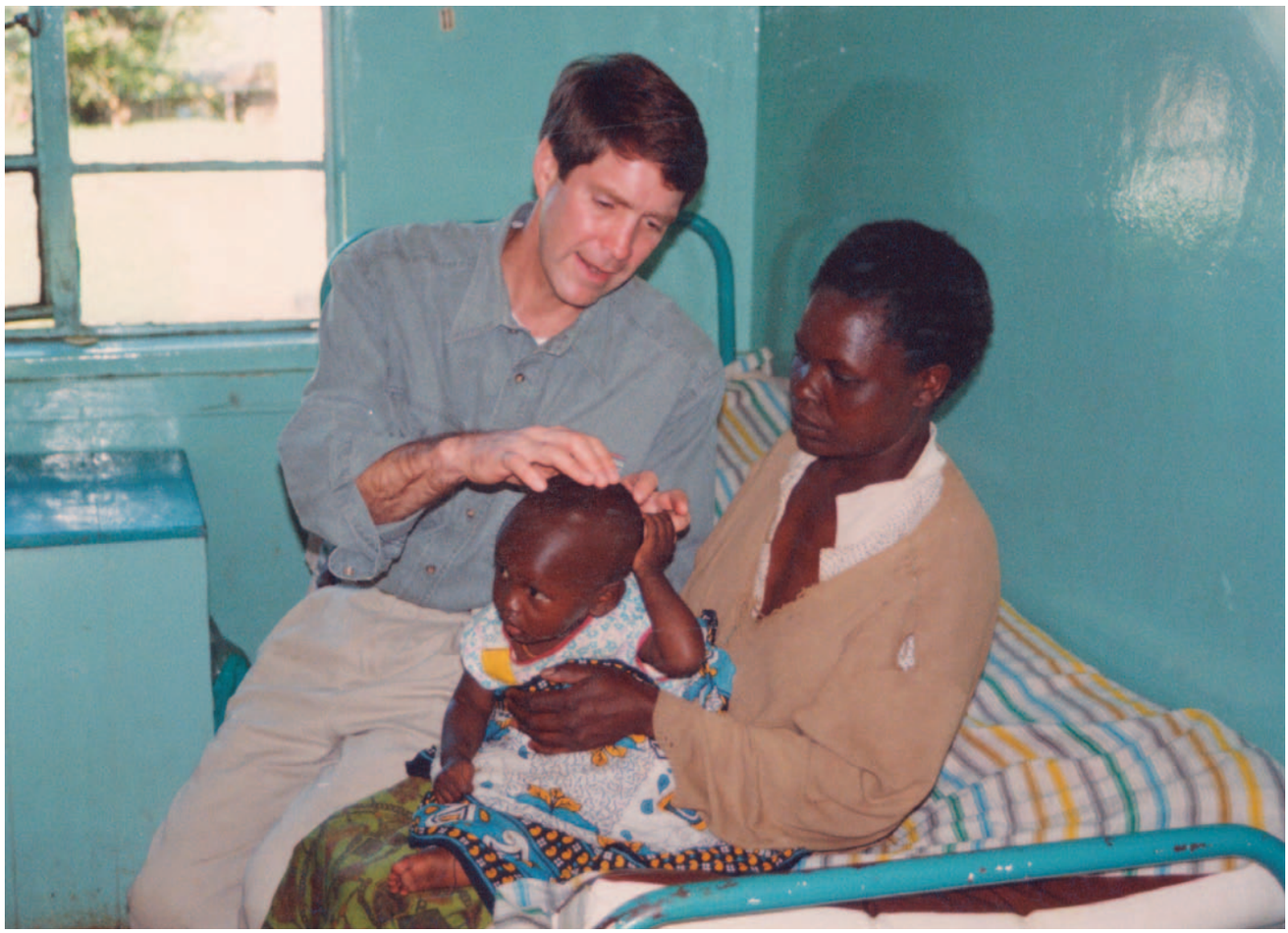
PHOTO COURTESY OF SAMARITAN'S PURSE



Bill Frist, M.D., examines a young patient at the Lui Hospital in southern Sudan during a recent medical mission.

Fighting viral infections

A scientific challenge and humanitarian imperative

By Bill Frist, M.D.

Bill Frist, M.D., is a United States senator from Tennessee and the Senate Majority Leader. He is a former heart-lung transplant surgeon at Vanderbilt University Medical Center.

The AIDS epidemic is the world's most urgent public health need. It is also the greatest humanitarian and moral crisis we confront. More than 40 million people are infected with the human immunodeficiency virus (HIV), which causes AIDS, a disease that kills more than 8,000 people every day, according to the World Health Organization.

HIV/AIDS has devastated economies, slashed in half the life expectancy in countries such as Botswana, and left millions of children orphaned, destitute and vulnerable to exploitation. The African continent alone is losing an entire generation, as 40 million children will be orphaned by AIDS in the next decade – a number equivalent to all American children living east of the Mississippi. By 2010, more will have died of AIDS than all those who perished in World War II, both civilian and military. And 90 percent of those infected do not know they have it.

Pictured below: Bill Frist, M.D., (in the foreground) performs surgery in the Lui Hospital, and poses with village children during a recent medical mission to southern Sudan. Every year Frist joins volunteer doctors from around the world to care for patients in the hospital, which is operated by Samaritan's Purse, an international Christian relief organization based in Boone, N.C.

Photos courtesy of Samaritan's Purse

Through a combination of government and private resources, the United States and other industrialized nations are rising to meet these challenges by aiding educational and public health efforts to prevent the spread of infection and funding to provide anti-retroviral drugs, which can extend life and preserve health in infected individuals.

Until science produces a vaccine, prevention through behavioral change is the key. Even in HIV-ravaged Africa, most of those tested for the virus will test negative. Thus, prevention presents a real opportunity to save countless lives. Access to inexpensive and rapid HIV testing can help reinforce prevention messages and guide treatment options. In Africa, I have personally witnessed how testing centers become centers of hope for the community, places where those struggling with HIV/AIDS can learn important coping strategies, receive nutritional and medical treatment, and support others with the disease.

Furthermore, we need to continue to develop ways to encourage people to get tested. In every nation of the world, stigma – the fear of discrimination – prevents many people from getting tested. Over the long term, we need to find ways to reduce stigma. For example, we must work toward developing guidelines for medical personnel to make HIV testing a more routine part of medical care.

Testing leads to treatment. And preventing new infections and saving lives through treatment are our two most important objectives. When people with AIDS receive nutritional and medical assistance, they live longer, healthier lives. They are more likely to avoid opportunistic complications such as pneumonia, tuberculosis and certain cancers.

Treatment provides additional public health advantages. Anti-retroviral treatment lowers the amount of virus in the body, potentially decreasing the risk of transmission, both among adults and between mothers and their children. New treatment regimens may make an even bigger difference in extending life and holding families together.

But much remains to be done. HIV is a cagey opponent, capable of mutating rapidly and outwitting the drugs that attempt to block it. While to date we still have not developed an effective vaccine, our best minds continue to pursue that noble goal. That is the basic research described in this issue of *Lens*.

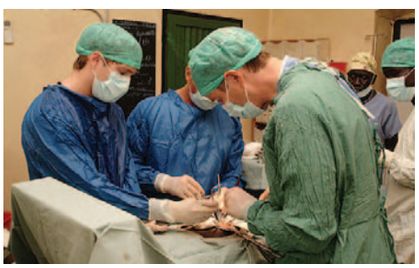
Basic research is also an essential part of our public health defense against emerging viral infections, like SARS, and against the danger posed by potential biological and chemical agents, such as smallpox or anthrax. Research can help us prepare by showing us how viruses damage cellular machinery, and how we might strengthen the body's immune system against these viral invaders.

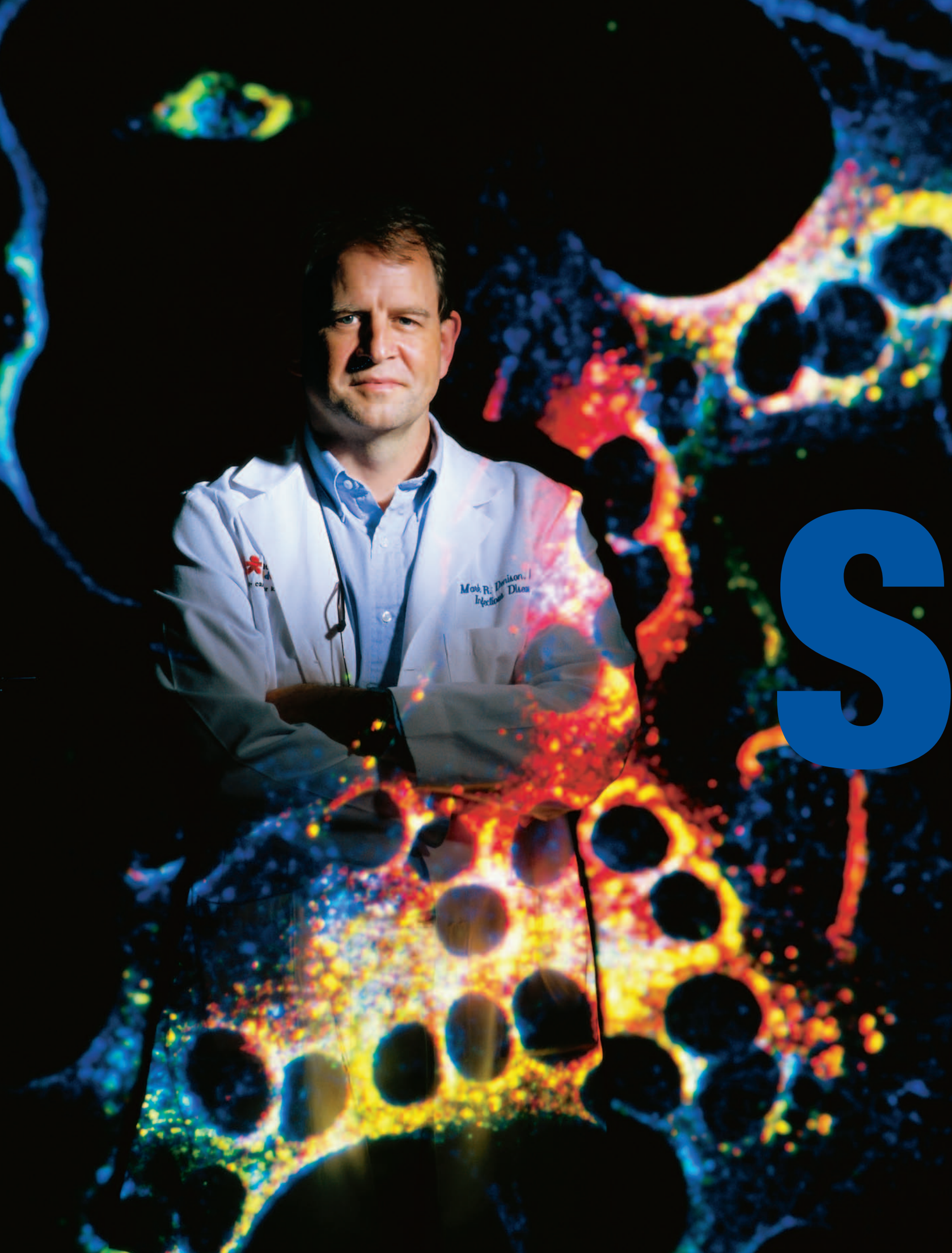
We must also look to those areas of the world that have achieved a level of success in fighting the spread of HIV/AIDS and seek to replicate their achievements. Uganda, for example, uses a distinctive approach to AIDS prevention known as ABC: Abstain, Be faithful to one's partner, and use Condoms. This program combines risk avoidance strategies (through partner reduction) with risk reduction strategies (through prophylactics) and has led to a decline in AIDS prevalence in Uganda, reducing infection rates from 21 percent to 6 percent since 1991.

Thirty years ago, with the success of antibiotics against bacterial infection and vaccines against polio and a host of other childhood infections, some experts predicted that medicine had conquered infectious disease. Unfortunately, our experience with AIDS, SARS and antibacterial resistance has shown that our battle against infectious disease is ongoing and ever-changing. For instance, even a well-known disease like influenza continues to kill 36,000 people in the United States annually. Given this challenge, we cannot relax or lose our focus; in fact, we must redouble our efforts to prevent, to treat, to understand and to cure.

This issue of *Lens* includes the latest information about HIV and SARS, the challenges of fending off serious viral illnesses in newborns, and the contributions of scientists like David Baltimore, Anthony Fauci and Harold Varmus, whose discoveries have added greatly to our understanding of viral infection. The persistence of these investigators in the face of obstacles that would have stopped the less determined should serve as an inspiration to us all.

The immense global challenges posed by the AIDS epidemic seem overwhelming, but working together we can overcome them because we must. That is the political and moral responsibility not only of the scientific and medical community, but also of humanity itself. **LENS**




Mark R. Denison, M
Infectious Diseas

Pictured left: Mark Denison, M.D., seems to be engulfed in a projected image of cells infected with a mouse coronavirus.

Photo illustration by Dean Dixon.

by Leigh MacMillan

SARS

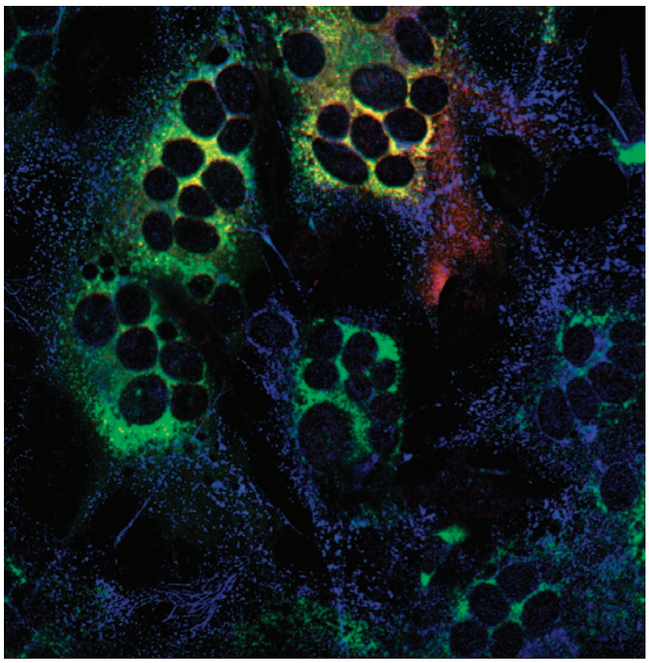
A narrow escape – at least this time.

For Julia, the 13-year-old daughter of Mark Denison, M.D., SARS was a passing fancy. In February 2003, before the world confronted a strange new disease – Severe Acute Respiratory Syndrome – she asked her dad why he didn't work on an important virus. After all, he'd been studying a coronavirus for nearly 20 years, and who had ever heard of coronaviruses?

Within a month, the world had heard: a new coronavirus was causing SARS. Denison, one of a handful of scientists who had studied the biology of this virus family, became a sought-after source of information for both public health officials and the media. Julia enjoyed that her dad finally was working on something important, but advised him that he was getting "kind of full of himself," he recalls.

By the fall, SARS was gone. An unprecedented global public health response had halted the virus' spread, continuing surveillance efforts were in place to quickly spot and address new cases of SARS, and scientists were searching for effective treatments and pursuing vaccine strategies. For Denison, associate professor of Pediatrics and Microbiology & Immunology at Vanderbilt University Medical Center, the experience was an unsettling near miss.

SARS, he says, represented "potentially the worst pandemic virus in the last 100 years. When you look at the overall severity and mortality rate of SARS and the rapidity of its spread, I'd say the bomb had started going off."



SARAH BROCKWAY

Pictured left: Confocal immunofluorescence image of cultured mouse brain tumor cells that have been infected with the mouse hepatitis virus, a coronavirus. The culture was mixed with a fluorescence-labeled antibody that specifically attaches to a viral enzyme. Confocal microscopy visualizes infected cells and virus-induced syncytia, or cell fusion, which enables the virus to slip from one cell to another.

A well-organized international public health response defused the crisis. In July – just four months after the World Health Organization first issued global alerts about SARS – WHO announced that the last chain of human transmission of SARS had been broken, ending the epidemic. The final tally: 8,422 cases of SARS and 916 deaths.

"The World Health Organization deserves an enormous amount of credit for the effectiveness with which they attacked the problem, with what you can only describe as 14th Century technology: quarantine," says John La Montagne, Ph.D., deputy director of the National Institute of Allergy and Infectious Diseases. "It worked, fortunately."

Even though its spread was stopped, SARS is still around. Swift isolation of this year's few victims and their contacts has quelled the virus – so far, there has been no transmission to contacts and the SARS patients have all recovered. But increased vigilance must continue, Denison says. SARS was a primer for the future's lurking viral threats: from it, we learned that global public health and rapid intervention mechanisms must be in place.

We were lucky with SARS, Denison maintains. Despite its high pandemic potential, the SARS coronavirus also had an Achilles heel that made it succumb to the infection control barriers erected against it. The next time around, we might not be so lucky.

Crown of spikes

In images from the electron microscope, coronaviruses look like the suns of preschool drawings – large circles surrounded by crowns of smaller dots. The crown, formed by the "spike" protein on the viral surface, gives the family its name.

Inside these spike-covered spheres is the coronavirus genome, one long chain of nucleic acids. While most organisms have DNA as a genetic material, coronaviruses – and other viruses including HIV and influenza – use RNA, a fact that makes them prone to mutation. The coronavirus genome, the largest-known RNA molecule, is translated in infected cells into a replicase polyprotein, which is snipped into smaller proteins that together mediate all of the different steps of making new viruses.

The replicase polyprotein captured Denison's interest nearly 20 years ago. He and Stanley Perlman, M.D., Ph.D., professor of Pediatrics and Microbiology at the University of Iowa, were the first to identify coronavirus proteins that were required for the virus to reproduce. Using tools such as monoclonal antibodies, antibodies made in the laboratory to recognize specific targets, Denison has continued to work toward a complete understanding of what the proteins are, how they're lined up within the larger polyprotein, and how they're cut apart.

"Sometimes it's been like working on a jigsaw puzzle where all the pieces are square, and they're all black, and I'm in a closet with the lights turned off," Denison muses. Adding to the difficulty, he says, has been the need over the course of his career to explain why he would choose to work on mouse hepatitis virus, one member of the coronavirus family. He recalls hallway conversations with colleagues that went something like: "You're a smart guy, Mark, why don't you study a different virus?"

It turned out that those studies were critical.

"When the SARS epidemic hit, Mark was among the first to realize that of the coronaviruses, SARS was most like mouse hepatitis virus," says Barton Haynes, M.D., director of the Duke University Human Vaccine Institute, and leader of the Southeast Regional Center of Excellence for Emerging Infections and Biodefense. The consortium of six universities, including Vanderbilt, is charged with developing the next generation of vaccines, drugs and diagnostic tests against emerging infections such as SARS, and for defense against organisms such as smallpox that might be used in bioterrorist attacks.

Denison "had already made many monoclonal antibodies against (mouse hepatitis virus) replicase," Haynes says. "Remarkably (they) reacted with SARS, and Mark had the first SARS monoclonal antibodies in the world. He continues to make

SARS was a primer for the future's lurking viral threats: from it, we learned that global public health and rapid intervention mechanisms must be in place.

China's painful lesson

China was roundly criticized last year for its handling of what are now viewed as the first cases of SARS and for under-reporting the true numbers during the outbreak. Lack of preparation contributed to the problem, asserts Jesse Huang, M.D., epidemiological advisor for the scientific group of the Chinese national SARS task force.

China's public health infrastructure is about 10 years behind the United States in terms of preparedness for emerging diseases, he says. But that situation is changing quickly.

Huang, former chief epidemiologist of Nashville's Public Health Department, returned to his native China last year to help bolster public health efforts there. Speaking from Beijing, he says, "China has really learned the importance of public health. It's like insurance; you just have to have it. Without the public health system, when you see something it's too late."

The SARS outlook in China is much better this year – the public is educated regarding infectious disease control, health care professionals are alert, and government agencies are poised to handle the situation, Huang says. These improvements are important for managing other emerging diseases as well.

"China has a lot of emerging diseases, and now China is much better positioned for encouraging and promoting international cooperation," Huang says. "Disease knows no boundaries. It's a very important outcome of SARS that the Chinese government now has transparency in terms of sharing infectious disease information."

– LEIGH MACMILLAN

major contributions to our understanding of SARS pathogenesis, and is already regarded as a world leader in the field of both coronaviruses and SARS in particular."

Besides the inherently interesting biological features of the coronaviruses, Denison says, they are important and widespread pathogens. Coronaviruses have long been known to cause severe disease in animals, particularly pigs, calves, and chickens. Two human coronaviruses are responsible for between 20 percent and 30 percent of cases of the common cold.

"They were important human pathogens; they just weren't severe or critical human pathogens," Denison says of coronaviruses before SARS.

But coronavirologists like Denison recognized the capacity of these viruses for trans-species adaptation. Over the last decade, he says, accumulating evidence has shown that coronaviruses can move between species "without too much fuss."

So when an ordinary coronavirus took a leap to human beings – most likely from a still unidentified animal source – and caused SARS, "I think coronavirologists were amazed, but not surprised," Denison says.

The leap appears to have happened in the southern Chinese province of Guangdong, where SARS-like illnesses occurred before the epidemic was acknowledged. Retrospective studies of patient records by Chinese and WHO epidemiologists have identified independent clusters of cases in seven Guangdong municipalities between November 2002 and January 2003. The absence of a link between these clusters adds weight to theories that the virus jumped to human beings from an animal species or other environmental reservoir in southern China, according to WHO.

The civet connection

In Guangdong China, wild animal markets and restaurants cater to the population's penchant for exotic fare – a made-to-order situation for putting people in contact with unusual animal viruses. Suspect animals in the SARS jump include the masked palm civet, a relative of the mongoose, and the raccoon dog, which are both consumed as delicacies in southern China and have been confirmed to be infected with the SARS coronavirus. In fact, the genetic sequence of the virus isolated from captive civets was nearly identical to that from the first confirmed SARS patient this year, prompting Chinese officials to order the killing of all civets – estimated at 10,000 animals – in the region to protect against further SARS cases.

Civets or raccoon dogs may have served as the conduit for transmission of the SARS coronavirus to human beings, Denison says, but the evidence is only circumstantial. "They may have just been bystanders – they happened to be in cage number three from the top, and whatever was on top was dropping virus all over everything below it."

Even if the civet is confirmed to be the culprit in transmitting the SARS coronavirus to human beings, eliminating contact with the animal will only go so far to prevent future outbreaks. The potential will still exist for animal coronaviruses – and other classes of viruses as well – to jump from animals to human beings.

RNA viruses, with their propensity for mutation, are especially likely to cause emerging infectious diseases, Denison says. The polymerase enzyme that copies the coronavirus genome, for example, has a high error rate – it makes lots of mistakes, resulting in virus particles with mutations. Some of these random changes may result in dead viruses, others may have no effect, and still others may make the virus better at infecting another species.

"Viruses don't 'respond' to things like antiviral drugs, antibodies, temperature … they're making changes all the time," Denison explains. "Viruses are incredibly adaptive.

"I like to picture a kind of 'king of the hill' model," he says. "You've got the dominant viral population at the top, and all the time these other viruses are being produced. It's like a coup d'etat-in-waiting – if circumstances change, there's another virus group there ready to depose the king."

A study published this winter in the journal *Science* demonstrates just how adaptive the SARS coronavirus proved to be. A consortium of Chinese scientists tracked the virus' evolution – the changes in its genetic code – during last year's epidemic by analyzing the viral genome in tissue samples from patients infected during the early, middle and late phases of the epidemic.

They found multiple SARS coronavirus strains present during the early phase, with wide variation in the outer spike protein used for viral attachment to host cells. As the epidemic progressed, the spike protein sequence stabilized, presumably to the form with the greatest capacity for infecting

Pictured here: The masked palm civet is a small mammal related to the mongoose that is sold in the animal markets of southern China and consumed as a delicacy. It has been implicated as a source of the coronavirus that has been transmitted to humans.

Norman Owen Tomalin/Bruce Coleman Inc.

A vaccine primer

Vaccines are designed to "teach" the body's immune system to recognize and fight off invading pathogens. They do this by mimicking a natural infection, because they look like disease-causing agents, either in whole or in part. Types of vaccines include:

Live, attenuated vaccines
Viruses aren't "alive" in the sense that they can reproduce by themselves; they must hijack the machinery of the cells they infect in order to make copies of themselves. By "live," scientists mean that the viruses used in these vaccines are still capable of infecting cells, but the viruses have been "attenuated," or weakened, so they cannot cause disease.

Viruses can be weakened by growing them in cells in which they don't reproduce well. As they adapt to their new homes, changing their genetic material in the process, they become less able to cause disease in their natural host. Live, attenuated vaccines can also be created using recombinant DNA technology to alter genes in the viral genome so the viruses can't replicate as well.

Live, attenuated vaccines are good teachers of the immune system because they closely mimic a true infection. But the possibility exists that the living microbes that make up such a vaccine might cause illness, particularly in immunocompromised individuals, or the attenuated virus might revert to a virulent form and cause disease. Some children may experience a very mild form of measles (generally a rash and fever) a week to 10 days after receiving the vaccine for measles, mumps and rubella. And because the attenuated virus in the oral polio vaccine can revert in rare cases to a more virulent form that can cause paralysis, only inactivated polio vaccines are now used in the United States.

Inactivated (killed) vaccines
Inactivated vaccines are produced by growing large batches of disease-causing microbes and killing them with chemicals, heat, or radiation. Inactivated vaccines are more stable and safer than live vaccines, but they usually stimulate a weaker immune response than live vaccines. Examples include vaccines for influenza, hepatitis A, and rabies.

Subunit vaccines
Subunit vaccines use only important parts of a microbe – the parts that will best stimulate the immune system. Because subunit vaccines do not include the entire microbe, they usually provoke fewer adverse reactions, but also a less vigorous immune response than live vaccines. Subunit vaccines can be produced by purifying proteins from whole microbes or by using recombinant DNA technology to produce the desired proteins in another cellular system. Hepatitis B and pertussis are subunit vaccines.

Toxoid vaccines
For bacteria that secrete a harmful toxin, the purified, but inactivated toxin – called a toxoid – can be used to stimulate a protective immune response. Examples include vaccines for diphtheria and tetanus.

Conjugate vaccines
Conjugate vaccines are a special type of subunit vaccine that link proteins to capsular bacterial material. The coupling of the protein to these bacterial substances renders the vaccines effective in young children. *Haemophilus influenzae* type B infections and pneumonia caused by *Streptococcus pneumoniae* are prevented by conjugate vaccines.

DNA/Recombinant vector vaccines
DNA vaccines introduce the genes that encode pathogenic proteins. After taking in the DNA – either in a "naked" form or shuttled in by a harmless virus or bacterium – cells in the body manufacture the proteins that will produce an immune response. These types of vaccines are in clinical testing for HIV, rabies and measles. At this time, none of the vaccines are being tested in children.

– LEIGH MACMILLAN

human cells, according to the team led by Guoping Zhao, Ph.D., of the Chinese National Human Genome Center in Shanghai.

The remarkable speed with which the SARS coronavirus adapted to human hosts underscores the importance of having robust public health systems in place that can recognize and defeat emerging viral threats before they sharpen their human attack skills.

Since the end of last year's epidemic, two cases of SARS associated with laboratory exposures have been reported, and a few apparently sporadic cases of SARS have occurred in China. Quarantine measures seem to have been successful – none of the cases became the focus of a new epidemic, and all of the victims recovered.

Much to learn

"We really don't understand why SARS came up in the first place, or where it's gone," Denison says. "There is certainly still a risk that it will reemerge as a severe pandemic disease, and based on that, there's a need to understand the virus and its emergence, biology, pathogenesis, treatment and prevention."

SARS has been called a respiratory illness – patients have usually presented with flu-like symptoms of fever, chills, aches, and coughing or breathing difficulty. Some developed hypoxia, with 10 percent to 20 percent of cases requiring mechanical ventilation. Most developed pneumonia. It appeared to spread by close person-to-person contact, probably involving respiratory droplets. But other features – a high incidence of diarrhea, the prolonged (seven- to 10-day) incubation period, and the mild disease in children – suggest to Denison that SARS might be a systemic disease, like measles, with a severe respiratory manifestation.

"We don't fully understand the pathology of this disease," he says.

So the world watches and waits. Surveillance programs, especially in regions that were hardest hit by SARS, aim to swiftly detect and isolate suspected SARS cases. In Hong Kong, for example, where SARS sickened 1,755 people and killed 299, every passenger entering or leaving the city – by any route – has been required since last summer to fill out health forms and pass in front of infrared cameras that measure the temperature of skin and clothing. Anyone with a fever must see a doctor.

But protracted surveillance at this level is an arduous prospect, and it may not catch the single case that starts a new epidemic.

"We learned from SARS that global interaction and the rapid exchange of information are very important for containing and controlling emerging diseases."

Larry Anderson, M.D., chief of the Respiratory and Enteric Virus Branch at the U.S. Centers for Disease Control and Prevention.

JAMES GATHANY/CDC

"Surveillance is a difficult thing; formal surveillance programs are often not located in the right place at the right time," says Larry Anderson, M.D., chief of the Respiratory and Enteric Virus Branch at the U.S. Centers for Disease Control and Prevention. Instead, for SARS and other emerging infectious diseases, the CDC and WHO rely on what's called the "astute clinician concept" – the idea that practicing physicians notice something odd, talk about it, pursue it and bring the information to the public health community.

"In light of that, what we've tried to do with SARS is provide opportunities to inform clinicians about when they should be concerned," says Anderson, who has been overseeing the CDC's SARS task force. The task force is responsible for coordinating the CDC's SARS activities, which include developing guidance, training and education documents, working on SARS diagnostic tools, interacting with the international public health community, and providing experts on site to assist in investigations.

"We learned from SARS that global interaction and the rapid exchange of information are very important for containing and controlling emerging diseases," Anderson says.

Only time will tell whether or not SARS will continue to be a pandemic threat. Denison suggests that awareness should be maintained for at least five years, maybe even 10 or more. In the meantime, funding has flooded into coronavirus research and the search is on for earlier diagnostic tools, treatments and vaccines.

Why invest in treatment and vaccine development if the SARS threat is uncertain? "It's about what we don't know, not what we do know," Denison says. "We don't know if SARS will reemerge as a more severe disease. It's too early to say."

Vaccine candidates

Current attempts to develop a SARS vaccine are pursuing multiple vaccine types (see page 8). These include a live, attenuated virus, an inactivated virus, purified viral proteins such as the spike protein, and recombinant virus vectors harboring one of the SARS proteins.

Denison and colleagues favor the live, attenuated virus approach based on the history of coronavirus vaccines in animals. Among multiple approaches that have been tried in different animal species, live, attenuated vaccines have been the most effective at generating a protective immune response in animal models. But because the virus is still capable of infecting cells, it can have undesired effects, among them reversion to a virulent strain or recombination with other viruses to make a new virus of unknown disease-causing capacity.

Denison argues that all of the various vaccine strategies must be pursued because we don't know how studies of animal viruses will translate to human beings. "Other investigators and I agree that inactivated virus strategies are likely the safest and may work," he says. "But they haven't worked anywhere else (in animal studies), so it's not wise to only pursue that approach – you'd put yourself way behind the curve."

Using a genetic system they developed for modifying the mouse hepatitis virus, Denison and colleagues plan to introduce mutations into the SARS coronavirus genome and assess the effects of these mutations on the ability of the virus to infect cells, reproduce and cause disease. Their goal is to create viruses that grow well in culture but do not cause disease, and which could be candidates for a vaccine. They've had success with this approach using the mouse hepatitis virus as a model.

If inactivated viruses turn out to be a viable strategy for vaccinating humans against the SARS coronavirus, Denison says their technique for modifying the viral genome would likely still be useful for safely growing the large quantities of virus needed to produce the vaccine. China is already moving to human studies of an inactivated virus vaccine, a government official announced in January this year.

"The amazing amount of work that has gone on since March (2003) is breathtaking," says the NIAID's La Montagne, who helped build the institute's successful influenza vaccine program and was the first director of the Division of AIDS. "I've never seen (the research) go this fast."

Denison smiles about the wealth of resources now being devoted to coronavirus research; it makes his scientific life easier, after all. But he hasn't forgotten his days in the trenches studying a virus no one thinks about.

"What this outbreak taught us was not just about coronaviruses," he says. "We need to understand the capacity of all kinds of viruses to move between species and the mechanisms by which they cause disease. We need to make sure that there are fundamental things that we know about all identified viruses – their genomic sequences, for example, and some basics about their biology."

Now that influenza has claimed the headlines, Denison says his daughter Julia wonders why he's not working on the flu virus instead. "I think she reflects the general attention span of the public for newly emerging viruses," he says. "But I live in this world because I understand that if we're successful – if we prevent disease through vaccination and other public health measures – people will say, 'What was the big deal?'" **LENS**

DEAN DIXON

Master of MICROEVOLUTION

The fight against HIV– a progress report

It has only nine genes, encoding just 15 proteins. Yet HIV – the human immunodeficiency virus – is a master of microevolution. So far it has evaded every attempt to subdue it.

Combinations of drugs that block key viral enzymes can reduce the "viral load" in the bloodstream to near-undetectable levels, allowing patients to live healthier, more productive, and longer lives. Yet no medical intervention has been able to flush HIV from the body or – through a vaccine – prevent infection from occurring in the first place.

by Bill Snyder

"It's highly complex, even though it's not a living organism," says Richard D'Aquila, M.D., who directs a new federally funded AIDS Research Center operated jointly by Vanderbilt University Medical Center and Meharry Medical College in Nashville. "It lends new meaning to the word parasite."

HIV is not "alive" in the sense that carries the instructions necessary to reproduce. Like other viruses, HIV must hijack the reproductive machinery of the cells it infects to make copies of itself. HIV is "sneakier" than many of its viral cousins, however. Through rapid adaptation to its changing environment, the virus rapidly mutates so that some of its progeny can escape the antibodies and anti-viral drugs that otherwise would neutralize it.

Another reason HIV is so hard to stop is that it attacks "helper" T lymphocytes, also called CD4 T cells, a type of white blood cell that "orchestrates" the body's immune response to microbial invaders. CD4 refers to a cell surface receptor to which HIV binds.

Like generals barking out orders to their troops, helper T cells send out chemical signals that "activate" the two major arms of the immune system. In one arm, B cells produce antibodies that can neutralize free-floating microbes and thus prevent them from infecting cells. In the other, cytotoxic T cells secrete a variety of toxic substances to kill cells that have already been infected.

Transmitted across mucosal barriers through sexual contact and by direct blood-to-blood contact, HIV relies primarily on a "Trojan horse" approach to reach its target host cell, the helper T cell.

The Trojan horses are the scavenger cells, including macrophages and dendritic cells, which patrol the mucosal borders. These "border guards" normally ingest and break down viruses or bacteria, and present peptide pieces of the foreign invaders on their cell surfaces to the helper T cells. When these viral antigens dock to cell surface molecules including the CD4 receptor, helper T cells begin proliferating and activate the immune response.

Somehow HIV escapes digestion by the scavenger cells and is presented intact – and thoroughly infectious – to the helper T cell. It hooks, and fuses with, the cell membrane and pulls itself inside. Then, like others in its family of "retroviruses," it hijacks the cell's reproductive machinery to make new copies of itself. *(See illustrations, pages 13 and 14).*

HIV replicates faster in helper T cells that are proliferating. "The virus is so in tune with how our immune system works that it's evolved to thrive in the exact circumstances that the immune system uses to try to beat it back," says D'Aquila.

Eventually, and it may take years, the population of helper T cells declines – some are killed by the virus; others by

(continued on page 14)

Pictured here: Richard D'Aquila, M.D., director of the Vanderbilt-Meharry Center for AIDS Research, holds a vial of fluid from HIV-infected cultures in the Biohazard Level 3 lab at Vanderbilt University Medical Center.

Secrets of a deadly virus

Steps in the life cycle of HIV offer clues to stopping its spread

Illustration by Dominic Doyle

Step 1:
The viral envelope protein, gp120, which is highly coated in sugars, docks to the CD4 receptor and a co-receptor on the surface of the T cell. This causes the envelope protein to change shape, allowing a previously hidden part of it, gp41, to "spring open" and seize the cell membrane like a grappling hook.

Step 2:
The viral envelope fuses with the cell membrane, and discharges the genetic core of the virus into the cell. A new class of "fusion inhibitors" can block entry of HIV by binding to gp41.

Other entry inhibitors are being developed. A cellular factor recently identified in monkeys, called TRIM5-alpha, may block un-coating of the viral shell or capsid after entry. TRIM5-alpha could lead to a new way to prevent HIV replication in humans.

Step 3:
Using nucleotides, or building blocks of DNA, from the cytoplasm, the viral enzyme reverse transcriptase *(pictured here as a zipper)* produces a DNA copy of the single-stranded viral RNA, then a second DNA copy. Drugs that inhibit the reverse transcriptase enzyme are a major part of existing anti-retroviral therapy.

Step 4:
The double-stranded version of the viral DNA is transported into the nucleus with the help of cellular proteins.

Step 5:
Another viral enzyme, integrase (*pictured here as needle and thread*), "sews" the double-stranded viral DNA into the cellular genome, at which point it is called a "provirus." Drugs are being developed to block the integrase enzyme.

In resting or "memory" T cells, the HIV provirus can remain silent for years. In T cells that are dividing as part of the immune response against HIV, the virus "commandeers" cellular machinery to transcribe thousands of copies of the viral RNA from the integrated provirus.

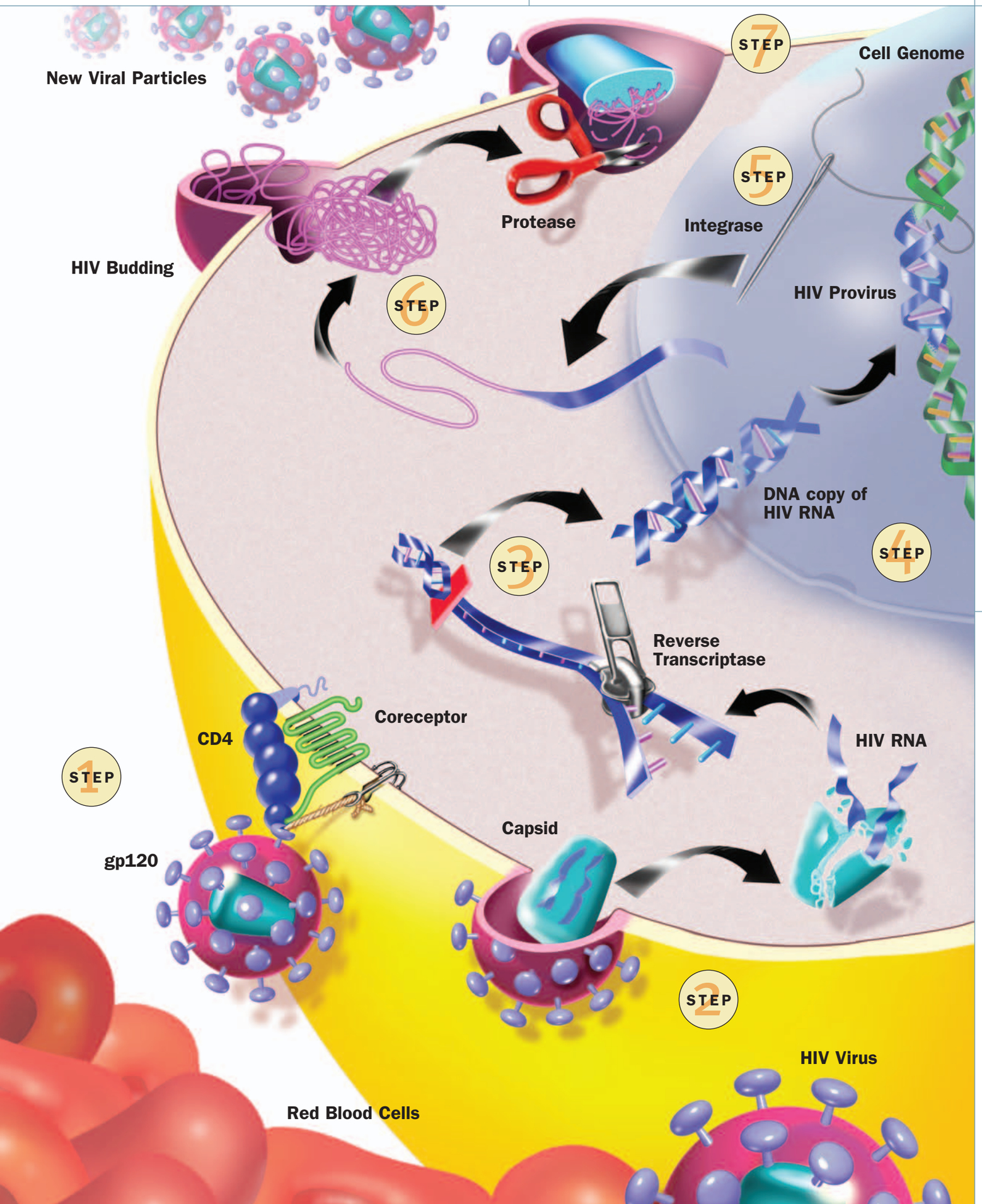
Step 6:
After transport to the cytoplasm, some of the RNA is translated – using the cell's protein-making machinery – into large polyproteins. Other cellular proteins transport the polyproteins to the cell membrane, and help construct a new virion.

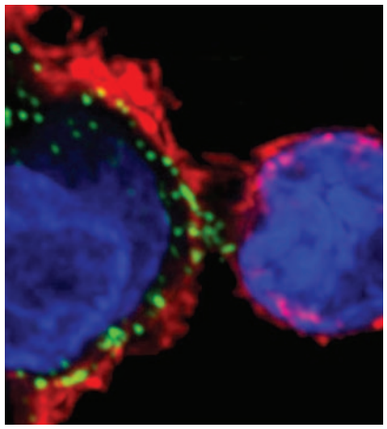
One of these proteins, called Tsg101, seems to be important in budding. "If you reduce the levels of Tsg101 in the cell, you see a lot of virions on the surface of the cell. They're trying to pinch off but they can't quite release," says Chris Aiken, Ph.D., associate professor of Microbiology and Immunology at Vanderbilt.

Step 7:
During the assembly process, the viral enzyme protease *(pictured here as a pair of scissors)* cuts itself from one of the polyproteins, and cleaves structural proteins necessary to form a functional viral core. Drugs that inhibit the protease are an important part of current anti-retroviral therapy.

At Vanderbilt, two recent discoveries may lead to ways to inhibit viral particle assembly and maturation. Paul Spearman, M.D., and his colleagues have found evidence of an as-yet-undetermined cellular factor that can inhibit particle assembly and release, but which is overcome by the viral protein U (Vpu). Identifying this novel cellular factor could lead to a new way to block HIV.

Meanwhile, Aiken and his colleagues are investigating a compound called DSB for its ability to prevent the protease from making an important cleavage in the polypeptide, thereby delaying virion maturation and reducing HIV's ability to infect cells. "It's a completely novel mechanism of action for a drug," Aiken says. "And it's very potent; it seems to be very selective. Things like that are out there. They will just need some decision makers in industry to say, 'Let's go after this.'"


New Viral Particles
STEP 7
Cell Genome
Protease
STEP 5
Integrase
HIV Budding
STEP 6
HIV Provirus
DNA copy of
HIV RNA
STEP 4
STEP 3
Reverse
Transcriptase
Coreceptor
CD4
HIV RNA
STEP 1
Capsid
gp120
STEP 2
HIV Virus
Red Blood Cells



Pictured here: Fluorescence microscopy captures the migration of green-labeled HIV particles to the junction between a dendritic cell (left) and a smaller T cell. Intact virus crosses the "infectious synapse" between the cells undetected, after which it takes over the T cell's machinery as a factory for its own reproduction.

Image courtesy of Thomas Hope, Ph.D., and David McDonald, Ph.D., University of Illinois at Chicago

(continued from page 10)

mechanisms that are not well understood. When the generals are taken out of the action, immune responses gradually become uncoordinated and ineffective even against weak invaders, called "opportunistic" infections, that otherwise would not gain a foothold in the body. The result: acquired immune deficiency syndrome (AIDS).

Mutating to survive

HIV is not without its vulnerabilities. There are now more than 20 different drugs or drug combinations that can block the actions of key enzymes necessary for viral replication. More drugs are in development. Resistance is a major problem, however.

Each time HIV copies its genome, on average one error, or mutation, is introduced. Some errors are crippling: the resulting viral particle is no longer infectious. But other mutations enable the virus to hide from the immune defenses that are trying to neutralize it, or become "resistant" to the drugs that try to block it. These are the viruses that survive and thrive – because they are the fittest. "There is almost no end to the ability of the virus to change its genetic structure," says Paul Spearman, M.D., co-principal investigator of the Vanderbilt HIV Vaccine Program. "It's definitely the most variable virus that we've ever encountered as a major pathogen."

Not every part of HIV mutates rapidly. Some regions of a viral envelope protein called gp120 are relatively stable or "conserved," though usually hidden from view. Gp120 exists as a trimer, three proteins bound tightly together in a sugar coat. When it binds to the CD4 receptor on the helper T cell, the trimer opens up, allowing further binding to a second "co-receptor" on the cell surface, and exposing the conserved region of the protein. Virus and cell membranes then fuse, allowing the viral contents to be "dumped" into the cell.

It's this more vulnerable part of gp120 that Spearman and his colleagues are targeting. They've begun animal tests of a "pseudo-virion," a fake (and non-infectious) viral particle, consisting of the gp120 trimer attached to the CD4 receptor in such a way that the normally hidden, genetically conserved and less mutable region of the viral receptor is exposed. The hope is that this potential vaccine will generate antibodies that recognize and attach to this viral "Achilles heel," thereby neutralizing the virus and preventing it from entering its target cell.

Other researchers are exploring ways to boost the effectiveness of cytotoxic T cells. Although HIV does not attack cytotoxic T cells (they bear another type of receptor, called CD8), their ability to rid the body of infected cells declines as the directions from helper T cells weaken.

Some people infected with HIV seem to be able to control the virus for long periods of time – even without drug therapy. "These are people who for whatever reason managed to get the upper hand very early," says Spyros Kalams, M.D., director of viral immunity at Vanderbilt, whose work helped define the critical interaction between helper and cytotoxic T cells in defending against HIV.

"I don't know why, but everything lined up the right way, and the virus was suppressed to low levels early, before it could do much damage," Kalams says. "We think that helper responses were preserved and they have great (cytotoxic) T cell responses and they're maintaining control."

Thanks to fluorescence-activated cell sorting, Kalams and his colleagues can separate – and study – distinct populations of T cells based on their tendency to proliferate and the fluorescent labels that have been attached to them. "What sort of receptors do they have? How well do they bind (to infected cells)? I'm trying to find the characteristics of each of these cells to see which ones might be the most effective at suppressing HIV replication," he says.

Recognition of the importance of cellular immunity has led to a new avenue of vaccine development – boosting cytotoxic T cell responses. In vaccine studies in animals, these responses do not prevent HIV from infecting cells, but they can slow down the course of the disease. "It is likely that a successful HIV vaccine will have to elicit both antibody and cellular immune responses," Kalams says.

Toward that end, Merck & Co., one of the world's leading vaccine manufacturers, is testing a circular bit of DNA called a "plasmid" that contains a viral gene. The plasmids are injected into muscle. Infected muscle cells are engulfed by the body's border guards, which transcribe and translate the genetic material into pieces of viral protein. The hope is that these antigens will activate cytotoxic T cells to attack HIV-infected cells.

A multi-pronged attack

At the National Institutes of Health, the Vaccine Research Center is developing a two-stage vaccine: a plasmid expressing modified genes that cover about 80 percent of the antigen content of HIV, followed by a booster consisting of the same genes carried in a harmless adenovirus. The genes are carried into cells by the adenovirus where they produce the simulated viral proteins that are processed and presented on their surfaces.

Taking the HIV shuttle

AIDS research could lead to advances in transplantation medicine.

Derya Unutmaz, M.D., and his colleagues at Vanderbilt are trying to prevent graft-versus-host disease, in which transplanted bone marrow attacks the tissues of the recipient, causing complications that can be potentially life threatening. Their goal is to "re-program" the transplanted T cells, using a modified, harmless form of HIV, so that the cells no longer recognize the recipient's tissues as foreign.

The researchers remove pieces of the HIV genome so it is no longer infectious, then stitch in genes for certain T-cell "transcription factors." The modified virus can still enter the T cell, only now it is a "shuttle," delivering genes that potentially can change the cell's behavior.

"We're really learning from the virus how the immune system works," Unutmaz says. "We think some good will come out (of) HIV."

In early studies in animals and uninfected humans, this approach has triggered significant increases in both cytotoxic T cells and helper T cells, says Barney Graham, M.D., Ph.D., chief of the Viral Pathogenesis Laboratory and Clinical Trials Core at the NIH Vaccine Research Center.

Combining a variety of HIV antigens into one vaccine may help prevent the virus from sneaking around the body's defenses by changing its highly mutable envelope protein. And it may provide protection against different "clades" or species of the virus. Graham hopes the vaccine may be ready for phase III clinical trials, which will measure its ability to reduce or prevent infection in high-risk individuals, by 2006.

HIV's resilience is due not only to its astounding ability to adapt to its environment. The virus also can hide from the immune system and drug treatment in the DNA of non-dividing T cells. When the cells are activated, years or even decades later, the previously latent virus re-emerges. "We have to find a way to identify this population so that we can target those cells directly or find ways to flush the virus out," says Derya Unutmaz, M.D., whose work at Vanderbilt has contributed to current understanding of HIV-immune cell interactions.

Another problem is that cellular proteins called transporters can prevent the drugs from even getting to the virus in the first place. Transporters are designed to keep cells clean, by pumping out toxic materials – but they also can eject anti-retroviral drugs.

Genetic differences in individuals also seem to play a role in the effectiveness of drug therapy, and the severity of side effects.

David Haas, M.D., principal investigator of the Vanderbilt AIDS Clinical Trials Center, and his colleagues recently reported that African-Americans are six times more likely than Caucasians to have a polymorphism, or genetic variation, that limits the ability of a cellular enzyme to break down a common AIDS drug. The result: higher levels of the drug and a greater frequency of neurocognitive side effects, including mental confusion.

All this makes therapy extremely complicated. Doctors must isolate the virus from their patients, determine its genetic sequence in the laboratory, and pick the drugs that are most likely to inhibit that particular strain of HIV. "It's individualized therapy," says D'Aquila, who helped pioneer HIV sequencing technology and resistance testing. "It's in constant flux. Every couple of months there's some new earth-shaking development."

The good news is that there are a lot of tantalizing leads to follow: natural factors and other compounds that can block HIV inside the cell; advanced technologies that enable scientists to "see" what's going on at the cellular and molecular levels; and new ways of boosting immune responses.

"I have great optimism that with some of the brightest minds of our generation focused on this problem, that we will have an effective AIDS vaccine," Haas says. "I envision one day in the distant future when we have a single pill that treats HIV in almost all people. But … the only way we're going to get to that is with continued, vigorous support of research." **LENS**

Promise and hope

Life as a teen-ager with HIV

When he was 9, Reggie Morgan Bragg stopped taking his medicine.

He was angry because – during delivery – he had been infected with the human immunodeficiency virus by his birth mother. He was mad because he had to take a handful of pills twice a day.

So he started dropping the pills behind the stove in the Nashville home he shares with his adoptive parents, Rod Bragg and Windle Morgan.

Two weeks later, while cleaning behind the stove, they stumbled on the hidden cache of medication. "There were just tons of pills back there," Bragg recalls. "The whole routine had gotten the best of him."

Now 13 and a gregarious sixth-grader, Reggie isn't angry anymore. "Being mad doesn't do anything," he says.

Reggie knows that without his medicine, he will develop AIDS and die. He wants to live, to play basketball with his friends, to grow up and perhaps become an architect.

"I'm glad they caught me," he says of his parents' finding his hidden medicine. "Now I'm having a happy life."

The number of babies born infected with HIV has fallen sharply in the United States during the past decade, thanks to prompt diagnosis and treatment of HIV-positive pregnant women – before delivery. But about 200 newborns still contract the virus from their mothers each year. There are plenty of young people like Reggie who are growing up with HIV – their viral "loads" controlled by a strict and expensive drug regimen.

They will always have to be careful about their health but – like Reggie – many are facing their futures full of promise and hope.

"He's a typical teenager with the energy and curiosity and the touch of rebelliousness that all young men and women have at that age," says his godmother, Rev. Mona Bagasao, chaplain and director of campus ministries at Eckerd College in St. Petersburg, Fla. "But he's been brought up to respect himself and other human beings … He's turned into such a wonderful young man."

"He's really touched my life and inspired me," says Reginald Hill, Reggie's sixth grade teacher at Jere Baxter Middle School in Nashville. "A lot of times I'll get frustrated, and I'll find myself thinking about him, and how I've seen him with a lot of his personal struggles. It makes me step back and say, 'Wait a minute. One day at a time.'"

ANNE RAYNER

Reggie Morgan Bragg with his cat, Feather.

Reggie "has a keen insight into the importance of education, that being the avenue for him to get to where he wants to go in life," his teacher continues. "With a lot of encouragement, a loving family, loving people around him, I think he believes he can do anything he wants to do. That makes us feel good. We want him to feel that way. The way medicine is changing, he may outlive a whole lot of us." – BILL SNYDER

PAUL FETTERS

unfinished business

AIDS, bioterrorism and the evolving legacy of Anthony Fauci >>

BY BILL SNYDER

The ghosts of 11 West haunt Anthony Fauci, M.D.

He can see the patients from the late 1960s, dying from an inflammatory disease that is now curable. He can feel the despair of the early 1980s, when the 11th-floor unit in the National Institutes of Health Clinical Center filled again – this time with patients in the final stages of AIDS.

The unit is nearly empty now. Most people infected with HIV live at home these days, thanks to advances in drug therapy. But at 63, the longtime director of the National Institute of Allergy and Infectious Diseases (NIAID) worries that something else is right around the corner.

"Last year we had SARS," Fauci says. "And then we had little blips on the radar screen … monkeypox … West Nile … Sooner or later, and likely in my lifetime, the next big one is going to come.

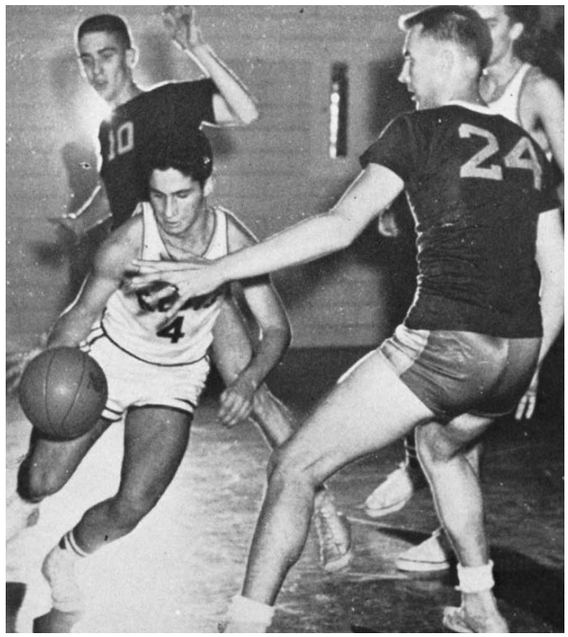
"We're much more ready than we were," he adds, his speech flecked with the accent of his Brooklyn upbringing, "but the way emerging and re-emerging diseases occur, you will almost never be totally ready, because it's a constant tension between emerging microbes and human civilization."

Pictured here:
At top, Anthony Fauci, M.D., stands next to Mother Teresa, winner of the 1997 Nobel Peace Prize for her work with the poor of Calcutta.

Middle photo, Fauci, class of 1958 and captain of the Regis High School basketball team, dribbles in for a basket against Brooklyn archrival St. Francis Xavier High.

Bottom, Fauci with his wife Christine Grady, R.N., Ph.D., and their daughters (from left) Alison, 11, Megan, 14, and Jennifer, 17.

Photos courtesy of the Fauci family.



PAUL FETTERS

For more than 20 years, ever since the first handful of cases of a strange pneumonia-like condition in gay men was reported by federal health officials, Fauci has been leading much of the government's fight against AIDS.

Along the way, he has advised presidents, been condemned – then applauded – by AIDS activists lobbying for lifesaving therapies, and become one of the world's most widely cited scientists for the important contributions he has made in immunology and HIV disease.

But he's not done. After Sept. 11, 2001, he launched an effort to develop countermeasures against a bioterrorist attack. He helped craft President Bush's $15 billion, five-year plan to combat AIDS throughout the globe. And he's dedicated to finding an effective HIV vaccine.

"He's a visionary. He knows where we ought to be," says Deputy NIAID Director John La Montagne, Ph.D., who has worked with Fauci since 1976.

Much of Fauci's success is due to his ability to communicate, adds his wife, Christine Grady, R.N., Ph.D., who heads human subject research in the NIH Department of Clinical Bioethics.

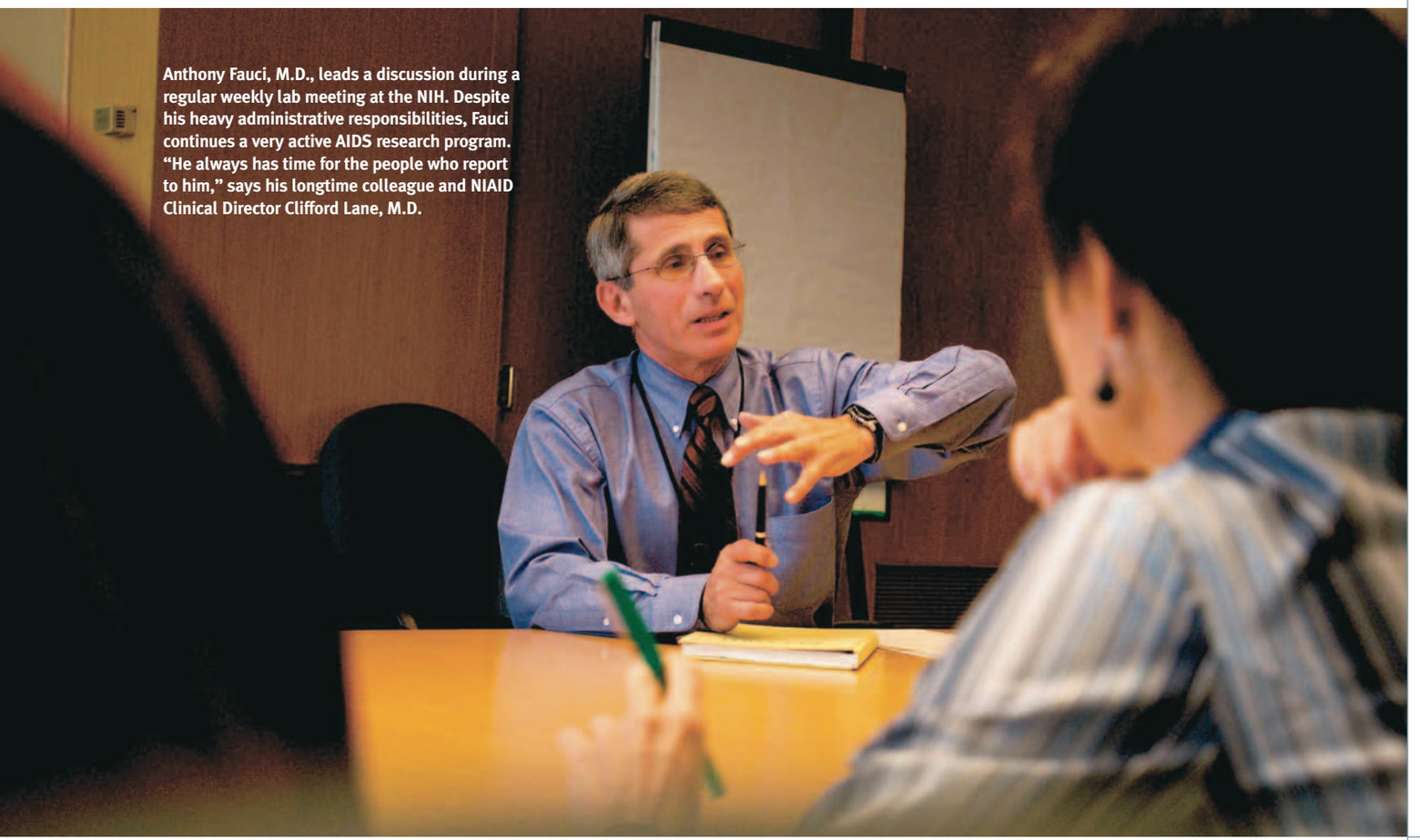
"He can take complicated issues and make them understandable to most anybody," Grady says. "He does it … in a clear and respectful way, and also with a lot of enthusiasm ... He can do that for members of Congress, he can do it for the fourth-grade science class, and he does both, or for an audience of virologists. That's perhaps his most enduring gift to society."

In his journey from the rough-and-tumble immigrant neighborhood of his youth to the top echelon of American science, Fauci has exhibited a remarkably unwavering sense of purpose and self-confidence. All along, he's been guided by a strong desire to discover new things, and to devote himself to public service.

>> Precision of thought

The grandson of Sicilian immigrants, Fauci grew up in the Bensonhurst section of Brooklyn. He credits his father, a pharmacist, and particularly his mother, who died when he was in medical school, for encouraging him to strive for excellence. The thirst for intellectual achievement was fueled by his Jesuit teachers at Regis High School, where he was captain of the basketball team, and later at Holy Cross College, where he learned – as he puts it – "precision of thought and economy of expression."

The Jesuit order of the Roman Catholic Church "is driven by intellectual curiosity – rigorous academic pursuits, openness and



Anthony Fauci, M.D., leads a discussion during a regular weekly lab meeting at the NIH. Despite his heavy administrative responsibilities, Fauci continues a very active AIDS research program. "He always has time for the people who report to him," says his longtime colleague and NIAID Clinical Director Clifford Lane, M.D.

honesty without having any intellectual constraints put on you," Fauci explains. The training prepared him well for life in Washington, where "you only have a very short time to express what it is that you need to express (and) to make it very, very clear," he says.

Medicine was a natural career path for Fauci, as it balanced his love of science with his need to be involved with people. He attended Cornell University Medical College (now the Weill Medical College of Cornell University), and as a young resident there, already was displaying strong leadership skills.

"He seemed to always have the ability to cut to the most important issue and describe a plan of action in a very direct way," recalls Steven Gabbe, M.D., dean of the Vanderbilt University School of Medicine, who was a medical student at Cornell when Fauci was a resident. "We'd have very, very sick patients. Tony would say, 'Here's the problem. Here's what we need to do, and this is how we need to do it.'

"He was a great teacher," Gabbe says. "I wanted to teach the way Tony taught."

In order to satisfy his Vietnam-era military obligations, Fauci joined the U.S. Public Health Service and after two years of residency was accepted as a research fellow into the lab of Sheldon Wolff, M.D., at the National Institutes of Health in Bethesda, Md. For Fauci, the NIH was the "hub of academic advancement and academic leadership."

Wolff, who directed the Laboratory of Clinical Investigation at the NIAID, was studying the molecular underpinnings of fever. Some of his patients with persistent or chronic, intermittent fevers had immune deficiencies, while others had vasculitis – blood vessel inflammation caused by a misguided attack by the body's immune system. Wolff encouraged his fellows to study a group of patients and find a way to treat them.

Fauci chose Wegener's granulomatosis, a severe form of vasculitis that was nearly always fatal. He recalls Wolff's reaction: "Let's sit down and try to figure out a protocol."

Upstairs, on the 12th floor of the Clinical Center, Vincent DeVita, M.D., who later became director of the National Cancer Institute, was testing drugs such as prednisone and cyclophosphamide – which suppress the immune system – to treat lymphomas and leukemias.

"We looked at the literature and came up with the idea: What happens if you treat these lethal inflammatory vasculitides with a low dose of these immunosuppressive drugs, not enough to wipe out the bone marrow but enough to suppress the aberrant immune response?" Fauci recalls. "And we did it in the first few patients and, lo and behold, they had a totally dramatic remission in their disease, which was just absolutely extraordinary.

"So then we started admitting a lot more patients, and a lot more, and . . . we ended up curing a very, very lethal, albeit uncommon disease." Fauci went back to Cornell to complete his chief residency in medicine in 1971-72, and after returning to Wolff's lab the next year, they reported their findings in 18 patients in the journal *Medicine*.

Wolff, who later became chairman of medicine at Tufts University before his death in 1994, put Fauci in charge of the lab's vasculitis program. "He launched me in my career," Fauci says. "I could not possibly have gotten to where I am right now had I not been put into an environment on this campus through the vision of people like Shelly Wolff who used the formula: 'Give me some smart people who are well trained and cut 'em loose.'"

Pictured right: Demonstrators demand quicker access to experimental AIDS drugs during the Reagan administration. Fauci, at the time the government's primary spokesperson on AIDS, didn't take the taunts personally. "I was seeing a bunch of sick people who were really scared," he recalls. "What they said made absolute, perfect sense."

Courtesy of Anthony Fauci, M.D.

>> Diabolical paradox

Fauci rose quickly through the ranks. He was appointed deputy clinical director of the NIAID in 1977 and chief of the Laboratory of Immunoregulation – a position he still holds – in 1980.

In the summer of 1981 came the first reports of unusual illnesses – pneumocystis pneumonia and Kaposi's sarcoma – in previously healthy gay men in Los Angeles and New York City. "I had a very sinking feeling," Fauci recalls. "I realized that these first few cases may really be something that is going to lead to a public health catastrophe."

Some of his colleagues were skeptical, but Fauci went right to work, changing the direction of his laboratory, and assembling a team to investigate what was beginning to be called acquired immune deficiency syndrome.

By 1983, Fauci and his colleagues had reported that the B cells of AIDS patients – the cells that normally produce infection-fighting antibodies – were inappropriately "hyperactive."

The causative agent, human immunodeficiency virus, would not be discovered until the next year, but the NIH group had described what Fauci calls the "diabolical paradox" of HIV – instead of being destroyed as most other microbes are by the immune system, the virus thrives on the attack.

"Since the immune system is the target, the very activation of the immune system makes it infinitely more vulnerable to being attacked because the virus more efficiently attacks an activated cell than it does a resting cell," he says. "It's a totally revolutionary concept, because you always think of the activation of the immune system as a good thing. Here it's like stepping on your own land mine."

Once the virus was described, and its sequence of nine genes determined, the NIH team – like thousands of researchers around the world – went to work to figure out how it wreaked such havoc, and what could be done to stop it.

In 1993, Fauci and his colleagues reported that even during the so-called "latent" phase of HIV infection, when little virus could be found in patients' blood, "the virus is continually replicating in their lymphoid tissue like a time bomb," he says. "Sooner or later it breaks down the immune system." The findings, published in the journal *Nature*, meant that physicians could not let up in their efforts to combat the virus – even when their patients seemed to be well.

Currently Fauci and his colleagues are exploring ways to boost the immune system in patients through the use of natural chemical signals such as interleukin-2.

In 1984, Fauci agreed to take on additional responsibility as NIAID director. "My goal was to have a broader impact on the field, not only of AIDS, but of all the infectious diseases and immunology," he told the NIH Historical Office in 1989. Impact it, he did. In the past 20 years, the NIAID has grown from the eighth largest at NIH, with a budget of $300 million, to the second largest, after the National Cancer Institute, with a budget of nearly $5 billion.

>> Including the activists

Fauci's new position also put him in the cross hairs of public attention. AIDS activists accused the government of ignoring those who were dying of the disease, and branded Fauci – the point man on AIDS for the Reagan administration – as an "incompetent idiot" and a "murderer."

In 1988, a group of demonstrators stormed the NIH campus, demanding quicker access to experimental drugs. Surveying the protesters, Fauci says he only saw "sick people who were really scared." Instead of calling in the security guards, he invited the leaders of the group up to his office. "I listened to them, and what they said made absolute, perfect sense," he says. "And that started a dialogue that led to the inclusion of the activists into many phases of our planning and advisory councils."

Fauci "is someone who is really trusted by all . . . people surrounding the AIDS challenge. I don't know of anyone as broadly accepted . . ." >> **Louis Sullivan, M.D., former HHS secretary**

About the same time, Martin Delaney, founding director of Project Inform, an AIDS advocacy organization, invited Fauci to San Francisco to see firsthand the plight of AIDS patients. Some were going blind because they did not meet the strict criteria to be included in clinical studies of an experimental drug that could save their sight. The experience convinced Fauci of the need to allow patients who wouldn't qualify for a clinical trial because of advanced disease to receive experimental drugs.

The U.S. Food and Drug Administration at first opposed the concept, called "parallel track," because of concerns it would make it more difficult to determine whether the drugs were safe and effective. But those fears were not realized; parallel track is now the model for testing new treatments for other diseases. "I give the activists a lot of credit for coming up with the concept," Fauci says.

"He is someone who is really trusted by all the different organizations and people surrounding the AIDS challenge, ranging from the scientific community, the academic community and the activist community," says Louis Sullivan, M.D., secretary of Health and Human Services during the first Bush administration and president emeritus of Morehouse School of Medicine in Atlanta. "I don't know of anyone as broadly accepted by all those disparate groups."

Since 1989, Fauci has been asked by a succession of presidents to become NIH director. He has declined every request, even when asked by President George H.W. Bush in the Oval Office. "If I took the NIH job, it would take me still one step further removed from what I really felt was the mission of what I wanted to accomplish," he explains, "namely HIV/AIDS, get a vaccine, get better drugs and then most recently, prepare the country with developing countermeasures for biodefense."

And at that job, he is seemingly indefatigable – regularly logging 80-hour weeks. "Dr. Fauci is absolutely reliable," says his longtime colleague and NIAID Clinical Director Clifford Lane, M.D. "If there is something that needs to get done, he will be sure it gets done, even if he has to do it himself.

"He always has time for the people who report to him," Lane adds. "If it's reviewing a manuscript for a younger person in his lab, something not many people at his level will do, … he will spend the time it takes to do it, which at times can be considerable."

What gives him such energy? "It is an indescribable experience," he told the NIH Historical Office, "knowing that what you are doing will have an impact on the lives of tens, if not hundreds, of millions of people." Yet he makes time to run every day, and to share a late dinner at least five nights a week with his wife and their three daughters, ages 17, 14 and 11.

In the midst of juggling his administrative duties and numerous speaking engagements, Fauci continues to do research and see patients on that historic 11th-floor unit. He is the quintessential physician-scientist. "If it were not for the basic research observations that are made," he explains, "the drugs that we have for HIV, the things we're doing with vaccines would never have happened."

And he continues to worry – about the next emerging infection, and about the vagaries of world politics that make it difficult to keep up the fight against AIDS.

"I think the United States has shown an incredible amount of leadership," Fauci says. "My concern is that the rest of the world doesn't step to the plate, and we miss a golden opportunity to have a major impact on HIV/AIDS. Because we have the tools now. We've got drugs. We know how to prevent it. We can do it. But we can't do it alone." **LENS**

"It is an indescribable experience, knowing that what you are doing will have an impact on the lives of tens, if not hundreds, of millions of people." >> **Anthony Fauci, M.D.**

PAUL FETTERS

Pictured right: Illustration of an influenza virus partially cut away to reveal internal structures. The green core contains the genetic information of the virus wrapped up in protein. This combination of genetic material and protein is called the nucleocapsid. Overlying the nucleocapsid is a layer of matrix protein, shown in purple. Over that is the viral envelope (blue-green and edged in yellow) derived from the host cell membrane. The nucleocapsid and the matrix proteins become wrapped in cell membrane as they bud from the infected cell. The characteristic "spikes" of the influenza virus are surface membrane glycoproteins, called haemagglutinin, that are involved in attachment and fusion to the target cell. They radiate all over the surface and are interspersed (in some types) by clusters of neuraminidase, another membrane glycoprotein that enables newly formed virions to bud from infected cells. These rapidly evolving glycoproteins are part of the reason flu vaccines must be adjusted to the prevailing influenza strains every winter.

Illustration by Ed Rybicki, Ph.D., professor of Molecular & Cellular Biology, University of Cape Town, South Africa. Copyright Russell Kightley Media, Canberra, Australia.

Cautionary Tale

New diseases, social factors challenge the victories of vaccines

Consider the myriad of diseases that once were, but are no longer, scourges in the Western Hemisphere: polio, smallpox, rabies, measles, mumps, rubella, whooping cough, Haemophilus. Within a few generations, these diseases, which used to account for thousands of American deaths each year, have been virtually eradicated from the population.

Attribute that to one of the greatest triumphs in the history of medicine – the use of vaccines to prevent the spread of dangerous disease. Ever since the 18th Century, physicians have known that inoculating patients with extracted, weakened doses of a virus enabled them to develop immunity to deadly outbreaks. From the mid-20th and continuing into the 21st Century, public health officials have initiated a national campaign to ensure that children receive a series of immunizations against specific microbes. The result, in terms of population health, has been phenomenal.

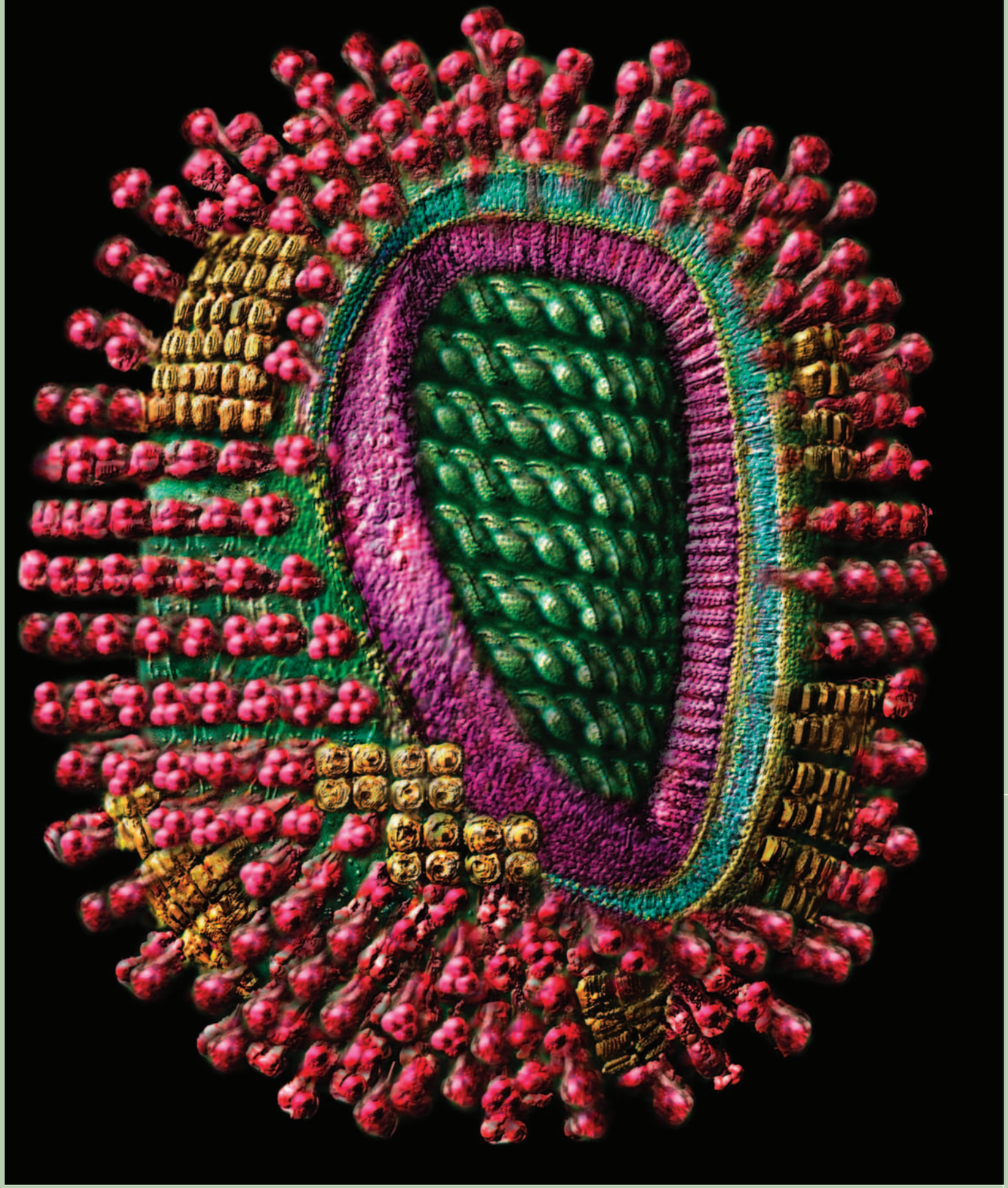
Ironically, vaccines have now become victims of their own success. "The most effective public health strategy of the century is under great duress," says Kathryn Edwards, M.D., who joined the division of Pediatric Infectious Diseases at Vanderbilt University Medical Center in 1980, and has subsequently worked on the evaluation and application of the *Haemophilus influenzae,* pertussis, pneumococcus, meningococcus, smallpox, and trivalent influenza vaccines. "When we see disease, we understand how important it is to prevent it. But the more successful we are with our vaccines, the more we (eliminate) diseases and people never see them. So they never fear them."

Because of some reports of bad side effects, a growing number of parents oppose having their children receive standard immunizations, such as the one against whooping cough. Yet without protection, pertussis can kill. Last year, four children died of whooping cough at Vanderbilt Children's Hospital.

Edwards says, "I really feel like the Maytag repairman. The better we are at preventing diseases, the more people are going to say these vaccines are bad. You can design an incredible vaccine, you can test it and know that it works beautifully and it's safe, but unless you get it into the arms of kids, it's a failure. So in this field you really have to think more programmatically, more practically and more about public health."

Pitfalls in the system of vaccine delivery have never been more apparent than during the recent influenza epidemic of 2003-04, when physicians and patients alike were caught off-guard by an early, startlingly virulent and widespread outbreak of the Fujian-A strain of influenza. Deaths from the virus and from secondary infections rose well above the "epidemic threshold" defined by the U.S. Centers for Disease Control and Prevention (CDC). An alarming number of these deaths occurred in previously healthy children. This was a scenario infectious disease experts have predicted and dreaded for some time.

By Lisa DuBois



While the global press has latched on to potential bioterrorism agents like smallpox and anthrax, experts in virology have warned that the next great pandemic, or worldwide outbreak, most likely will be an influenza. "In many ways flu is the scariest disease there is," says Edwards. "In contrast to AIDS, where you have to exchange blood or some sort of secretions, flu you get by what you breathe. It's respiratorally spread, and in a moment a virus that's in a pig lot in China can suddenly be in Los Angeles – and then all over the country."

One of the most devastating pandemics of all time was the 1918-19 flu, which killed 500,000 people in the United States and over 20 million worldwide. The greatest death toll was among healthy young adults. An accepted theory is that the pandemic was caused by the movement of troops during World War I, but Peter Wright, M.D., who heads Vanderbilt's Pediatric Infectious Diseases division, believes the answer may not be that simple. "The pandemic occurred equally in women," he explains. "And I had occasion to look at the public health records in Iceland, and the same pattern of deaths occurred in Iceland, which was pretty isolated from the effects of World War I."

Depending on a population's level of immunity to a particular strain and to subtle changes that occur in a virus' makeup, he says, influenza has a capacity to be more or less virulent and more or less deadly.

ANNE RAYNER

Kathryn Edwards, M.D., (seated, left) and Marie Griffin, M.D., (seated right) review findings from a vaccine surveillance study with research nurse Ann Clay, R.N., (standing left) and Diane Kent, R.N., (standing right), study coordinator.

Influenza virus types A, B, and C are classified based on the antigenic differences between two surface glycoproteins, H and N – hemagglutinin, which facilitates entry of the virus into host cells, and neuraminidase, which assists in the spread of infection. To illustrate just how insidious these antigenic changes can be, the 2003-04 vaccine contained protection against the H3N2 Panama-A strain, but not against its noxious H3N2 Fujian-A cousin that emerged too late to be included in doses manufactured for the season.

Most of the flu viruses that are emerging today originate in China and areas of the Far East where crowded, open air, poultry and meat markets create a prime breeding ground for viruses found in fowl and other animals including civets, small mammals that have been linked to SARS. These viruses constantly reassort and recombine their genes, creating new strains, some of which are pathogenic to humans. If influenza's surface proteins were as stable as mumps or rubella's, for example, one vaccine would offer lifetime protection. Instead, flu strains mutate quickly and unexpectedly, and antibodies against one strain don't necessarily provide immunity to the next year's outbreak. Public health officials, under the aegis of the World Health Organization and the National Institutes of Health, meet annually in Geneva to evaluate which pathogens are appearing on the scene, and to commit to developing vaccines for the upcoming crop of viruses. In other words, getting a good flu vaccine in any given season is like shooting a moving target.

Once the group identifies three dominant viral strains, pharmaceutical companies estimate the number of vaccines needed around the world and grow them in chicken eggs, a time-consuming technique that has been used since the 1940s.

Reverse genetics

Speaking from Hong Kong, where he is part of the WHO surveillance team, Robert Webster, Ph.D., an infectious disease expert at St. Jude Children's Research Hospital in Memphis, claims scientists knew Fujian-A was in the human population as early as February 2003, but they couldn't grow it in time for a vaccine. Had they been able to use a technique known as "reverse genetics," he insists, Fujian-A would not have wreaked such havoc.

The current technique for developing a vaccine requires six months, and tens of millions of eggs. Scientists produce a "viral seed strain" by reassorting two currently circulating viruses. With reverse genetics, scientists can rapidly engineer the seed strain in the laboratory by picking and choosing the H and N genes they want. In this way, they can custom design a vaccine that will be safe for humans, but which will also generate an immune response. The virus still must be grown in eggs to produce a vaccine, but the process can be completed in weeks instead of months.

"We have the technique for reverse genetics," Webster says, "and it could have been used this year, but it's not an approved method yet. We have to get approval for using that technique to generate vaccines quickly." The flu vaccine shortage that occurred this winter "is just the tip of the iceberg," he says. For example, a strain of avian flu even more virulent than the one that spread through Asia this winter could appear in the United States and cause more illness and death than the Fujian-A strain did. He adds, "If we get one of the new strains we're seeing in animals in Hong Kong, and if you think we're going to have plenty of vaccine in the face of pandemic, think again."

Part of the problem, says Marie Griffin, M.D., a pharmacoepidemiologist and professor of Preventive Medicine at Vanderbilt, is that the burden of disease from influenza has, historically, been under-appreciated. The past three or four flu seasons have been mild, so Americans didn't rush out to get a flu vaccine, and manufacturers threw away millions of excess doses last year. Each year influenza causes around 40,000 excess deaths, mostly in people over the age of 65, many of whom have other chronic illnesses. However, annually around 20 percent to 40 percent of children, who may be immunologically "naïve" to a new flu strain, also come down with influenza.

"What tips the balance toward our recommending that children get vaccinated is that some of those kids have severe consequences from flu," Griffin says. "What we're learning, or maybe learning again, is that there are quite a few kids under the age of two who end up getting hospitalized for influenza, which is a bad outcome even if few of those kids die."

Recent data indicate that in an average year, not a virulent year like the current one, one or two children per thousand, who are under age two, may be hospitalized with flu. Even more surprising, according to a recent unpublished CDC-sponsored study by Griffin and Edwards, 74 percent of infants and toddlers hospitalized with

(continued on page 26)

Polio

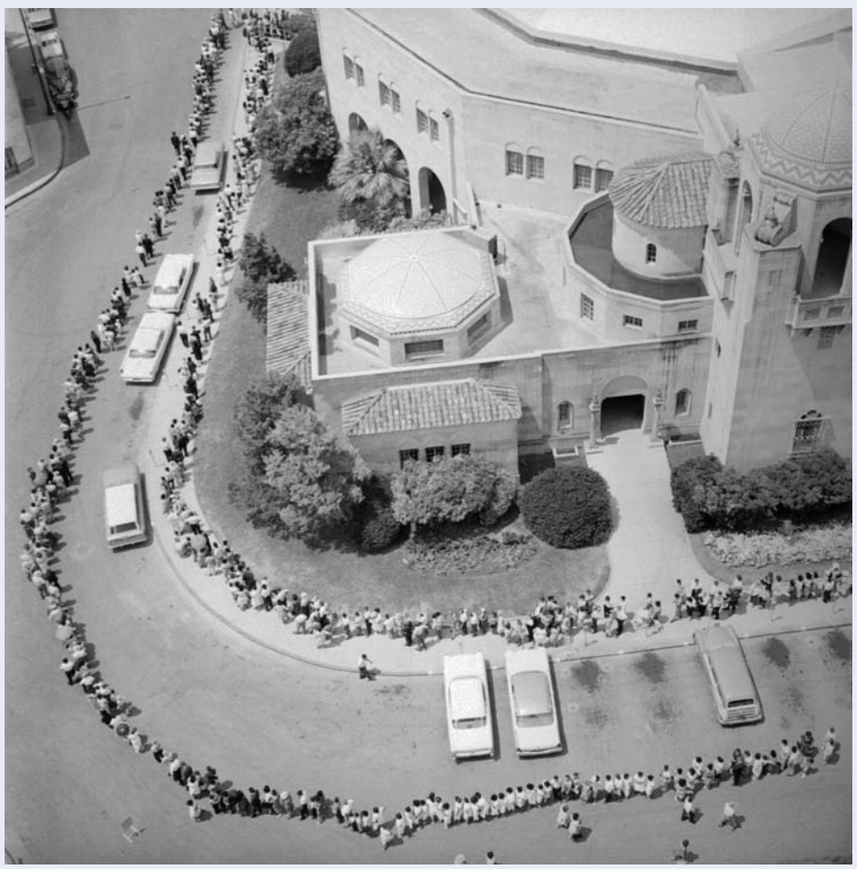
The fight continues

by Lisa Dubois

The near-eradication of polio is one of the most remarkable public health achievements in the history of the world. Yet, ironically, nearly 50 years after an effective polio vaccine was first introduced, public health officials are now faced with re-fighting a battle they thought they'd already won.

The poliomyelitis virus is extremely infectious, spread through fecal-oral or oral-oral transmission, replicating in the pharynx and gastrointestinal tract, then crossing into the central nervous system where it can destroy motor neurons and, in 1 percent of cases, leave its victims paralyzed. In the first part of the 20th Century, polio was responsible for a series of terrifying epidemics in the United States, including one that lasted from 1943 to 1956, in which 400,000 people were infected and 22,000 died.

STAFFORD SMITH/CDC



Hundreds of people – waiting for their oral polio vaccinations – line around the city auditorium in San Antonio, Texas, in 1962.

People 50 and older remember polio. They remember friends and classmates who were stricken with the disease, healthy kids who died suddenly or were left paralyzed or crippled. They remember being forced to stay inside during the summer months, warned against swimming pools and large crowds. And they remember the treacherous iron lung machines that kept children breathing through artificial ventilation.

America remained in the grips of this disease until Jonas Salk, M.D., introduced the inactivated polio vaccine in 1955. Six years later, Albert Sabin, M.D., developed a live oral vaccine, clearing the way for mass inoculations. In communities across the country hordes of people headed to local churches, gymnasiums or meeting halls, forming lines that wrapped around city blocks, for the chance to swallow a sugar cube with a dollop of pink vaccine on top.

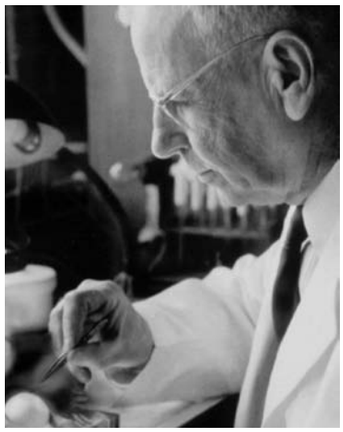
With dramatic speed, polio began to disappear. In 1960, 2,525 cases of paralytic polio were reported in the United States. By 1965, there were only 61. The last case of wild-virus polio in this country was in 1979, when the disease was imported from the Netherlands and members of Amish communities in several states were infected.

As polio began to fade away in the United States, the World Health Organization (WHO) and other groups turned their attention to other nations. According to the CDC, a polio eradication program conducted by the Pan American Health Organization succeeded in essentially wiping out the disease from the Western Hemisphere as of 1991. Polio is now endemic in only six countries – India, Pakistan, Nigeria, Afghanistan, Niger and Egypt – with 667 paralytic cases in 2003, 300 of which occurred in Nigeria.

Unfortunately, WHO recently suffered a setback in its initiative to eliminate the disease from the planet by 2004. Islamic clerics in northern Nigeria suspended polio immunizations after claiming the vaccine was contaminated with contraceptives and HIV. The suspension contributed to a resurgence of polio in the area, including several cases in neighboring countries. Earlier this year, after two independent labs found no evidence of contamination, Nigeria's president Olusegun Obasanjo pronounced the vaccine safe. Suspicion about the vaccine continues, however, and also has hampered immunization efforts in parts of India.

Faced with these new challenges, the Global Polio Eradication Initiative – a coalition of governments and international health and humanitarian organizations – are redoubling their efforts to achieve a world free of polio by the end of the calendar year. **LENS**

Ernest Goodpasture and the Mass Production of Vaccines



SAMUEL PAPLANUS, M.D.

In 1796, the English doctor Edward Jenner inoculated the 8-year-old son of an itinerant farm hand with the cowpox virus. Two months later, and on several subsequent occasions, he deliberately exposed the boy to fresh smallpox sores. Just as Jenner suspected, the boy never developed smallpox because his early exposure to cowpox – a related virus that does not cause disease in humans – provided lifetime protection against its more dangerous relative. Questionable ethics aside, Jenner is generally considered a medical pioneer – proving that vaccination could protect against a lethal disease.

Even though such world leaders as Napoleon Bonaparte and Thomas Jefferson were advocates of vaccination as a prevention strategy, most people feared the process – and with good reason. Many attempts at immunization failed because some patients developed fatal smallpox or serious bacterial superinfections. Also, far-fetched rumors circulated about children who were stricken with mange or an "ox-faced deformity" after being inoculated with cowpox. As a result, vaccinations were not generally accepted until well into the 20th Century.

In 1924, Ernest Goodpasture, M.D. was recruited to Vanderbilt University Medical School as its first chairman of Pathology. Interested in the pathology of viruses, he began to study the effect of herpes and rabies before turning his attention to fowlpox, which he preferred as a laboratory model because it was harmless to humans and it produced skin lesions in chickens that could be systematically evaluated. To expand his studies, Goodpasture had to figure out a technique for obtaining large quantities of fowlpox virus in pure culture.

Solving the problem, he and his colleagues, Eugene and Alice Woodruff, developed a method for growing the virus in chicken embryos, maintaining sterile conditions while they opened the eggshell and infected the underlying membrane with fowlpox. Using this chick embryo system, they consistently produced pure cultures of fowlpox.

"That was the first time viruses had been grown in a reproducible way in a pre-antibiotic era," says Robert Collins, M.D. professor of Pathology at Vanderbilt and author of the biography, *Ernest William Goodpasture: Scientist, Scholar, Gentleman*. "On the basis of his success with fowlpox, Dr. Goodpasture immediately began to work on vaccinia (like cowpox, another relative of smallpox), because he recognized the need to have a more standard vaccinating material against smallpox. He had found a relatively easy way to grow mass quantities of infectious material in a sterile environment. This was a major accomplishment in those times before tissue culture techniques were standardized."

In 1935, in cooperation with the Tennessee State Board of Health, Goodpasture and colleagues vaccinated nearly 1,200 children with the new smallpox vaccine and achieved a remarkable rate of success. But Goodpasture was a basic researcher, and realizing the potential for his landmark discovery, he simply handed the chick embryo technique for growing vaccinia virus over to Upjohn Pharmaceuticals to carry out its commercial production and delivery. Subsequently, the chick embryo technique was also used in the development of vaccines against yellow fever, typhus, influenza and Rocky Mountain spotted fever.

"In my view Goodpasture was an ideal academician," Collins says. "He chose the profession of medicine because of his desire to understand the mechanisms of disease and thereby reduce the ravaging effects of infections. And he recognized that academic medical institutions were in a particularly advantageous position to benefit mankind."

The "science, art and humanity" of an affiliated medical school, Goodpasture once stated in a speech, are of great benefit to universities. "Medicine," he said, "is the most universally accepted example of what education and science can do in the interest of well-being …" – LISA DUBOIS

(continued from page 24)

flu were otherwise healthy and not considered "high risk" for complications.

The CDC estimates that the annual associated costs from influenza – including doctor visits, hospitalizations, medicines, days lost from work, child care, etc. – exceed $12 billion a year. Moreover, the burden of disease from children with the flu is actually greater than that in people over 65. Griffin says that new rapid viral diagnostic tests have also raised awareness about how much flu is in the population at any given time.

The obvious solution would be that all people of all ages, who can safely do so, should receive all vaccines all of the time. Unfortunately, obstacles to the production and delivery of vaccines make that impossible.

FluMist, the nasal mist vaccine that uses a live, attenuated virus, was actually developed 10 years ago, but only became available to the public in 2003. One reason for the delay is that any new vaccine must first be tested in 30,000 to 40,000 people before it is approved for general use, making clinical trials extremely expensive and cumbersome. Another issue is vaccine safety.

"No one is willing to tolerate any kind of adverse event anymore," Edwards says. "The reason the nasal flu vaccine is not licensed for kids under five is because some kids who'd gotten the nasal flu vaccine had some wheezing – although it's probably the best way to vaccinate little kids. We're in a real bind because we need to be innovative, but we have more controls and more obstacles to licensing products."

"One of the things going on in vaccine development today is that we are taking on harder targets to immunize against," says James Crowe, M.D., associate professor of Pediatrics at Vanderbilt and an expert on respiratory syncytial virus (RSV), the leading cause of lower respiratory tract disease, such as wheezing and pneumonia, in infants under two months of age. Rather than target viruses that spread through the blood, such as measles, investigators are now trying to attack viruses like RSV that cause disease at the mucosal surface but never enter the blood – a much more difficult proposition, Crowe says.

Targeting children

An experimental inactivated RSV vaccine candidate developed in the 1960s enhanced rather than prevented disease, and was not further studied in humans. Newer, safer live, attenuated vaccine candidates can generate a good immune response in

JONATHAN RODGERS

Pictured right:
Peter Wright, M.D., chief of Pediatric Infectious Diseases at Vanderbilt, ponders a question from Haitian physician Sonia Jean, M.D., during a recent visit to Port-au-Prince. (*See related story, page 32*).

children older than six months, but not in younger infants – those at greatest risk for complications from RSV infection.

Crowe explains, "We believe that at the time of birth babies are in transition from an environment in which they are not exposed to foreign antigens to one where they immediately need to start making antibody responses. It may be that the answer to how to induce better immune responses in children is to give vaccines more frequently very early in life, so that we catch children at a time point when their immunologic development is moving along. The whole public health infrastructure would have to be reoriented for vaccines that have to be given more than once during the first month of life. We're currently not set up to do that."

As researchers work to create a vaccine against HIV/AIDS, infrastructure issues become even more problematic. Comprehensive studies show that in developing countries such a vaccine would have to be targeted towards 12- to 15-year-old children, who are not yet sexually active. To date, there is no effective AIDS vaccine, and the pressure is mounting to find one. Says Wright, "Perhaps the new antiretroviral drugs can slow an epidemic, but I don't think anyone will make a projection that HIV will go away without a vaccine component. The cost of AIDS in the countries of Africa where 10 percent to 15 percent of the young adults have HIV is of great interest to the U.S. government." He cites the potential for social disruption and political instability if such a large number of the most productive members of a country's work force becomes sick. "It is appropriate to take those costs into account as we introduce new vaccines," he says.

In fact, cost and liability, rather than scientific know-how, have become the greatest barriers to vaccine production. Even minor side effects and reactions from new vaccines are likely to result in lawsuits, a liability that vaccine manufacturers are unwilling to bear. The government will have to pick up the tab. Says Webster, "There used to be five manufacturers of flu vaccine in the United States. Now there is only one company manufacturing the standard injectable, and one making the nasal mist vaccine. I would like to send a message to our nation's legislators: If you want to have a vaccine in the face of a pandemic, then you'd better consider the liability issues now."

Vaccines, Edwards explains, are not like other drugs. A drug to prevent ulcer disease, for example, will be taken by millions of people over the course of years, whereas people may take a particular vaccine only once in a lifetime. "So the market share for vaccine is totally different than the market share for a pharmaceutical," she says. "The incentive to make new, sexy vaccines that could use incredible technology is not what it is for pharmaceuticals. Coupled to that, a lot of vaccines are given to children – and children don't vote."

In addition, Americans are used to purchasing their vaccines at bargain basement prices, since the government purchases half the vaccines available in this country. Edwards says, "If you work for a pharmaceutical company, you have to ask why you should be investing resources in a vaccine you give once a year to part of the population, and sell it to half those people for cost."

The public health response to SARS proved that scientists are becoming more adept at mounting dramatic research responses to the sudden emergence of traumatic diseases. They are less skilled at maintaining public support while they prepare for the next viral pandemic, which typically surfaces every 50 years or so. Should such an incident take place, a well-oiled system for manufacturing and delivering vaccines will be crucial to saving millions of lives. Such a system does not yet exist.

If there is a plus side to the cloud of bioterrorism that hangs over the Western world, it is that governments are infusing money into public health to address potential threats of epidemics and pandemics. "The flu provides a good model for testing how well we respond to major outbreaks of disease," Griffin says. "We now know much more about what we need to do and where the gaps in the system are."

One of those gaps, she says, is the under-use of effective antiviral medications, which have tended to be under-prescribed by physicians and under-tested in various populations.

Webster echoes that sentiment, insisting, "We need to begin stockpiling antiviral flu medicine. Because flu strains mutate so quickly, it won't help to stockpile flu vaccines, but the flu drug is effective against every single strain of flu we've tested it against. Legislators have to put that on their radar screens. The precursors, the viruses, for a pandemic like the one in 1918, are out there."

Still, Edwards believes there is reason to hope. "The more we continue to prepare for a disease, and particularly for a bioterrorism event," she says, "the less likely it is it will happen." **LENS**

Mary Beth Gardiner contributed to this story.

Q & A

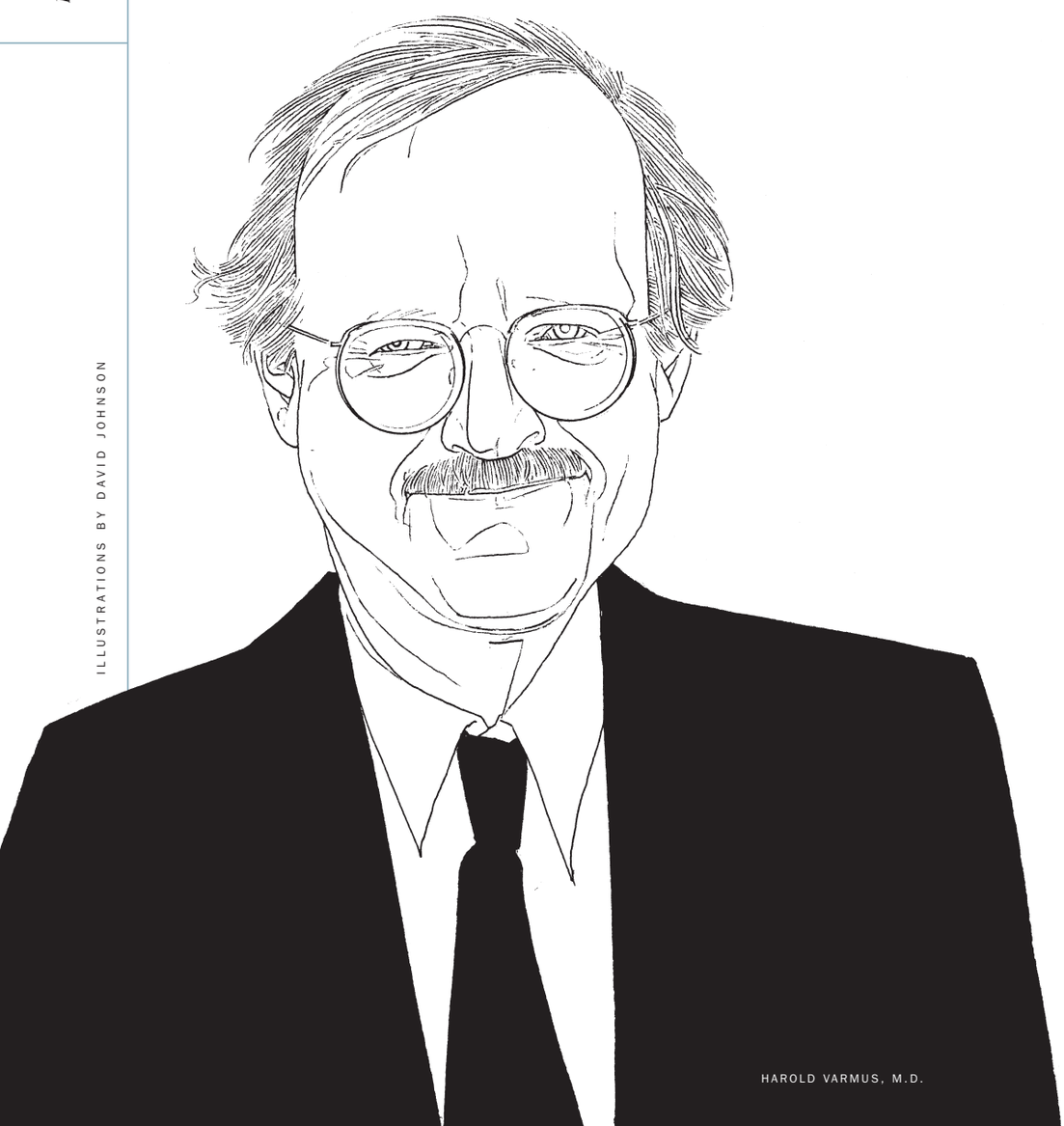
Pictured lower left: Harold Varmus, M.D., is president of the Memorial Sloan-Kettering Cancer Center in New York City, and former director of the National Institutes of Health. He shared the 1989 Nobel Prize with Michael Bishop for their discovery that the oncogene of the Rous sarcoma virus was not a true viral gene but was a normal cellular gene, which the retrovirus had acquired during replication and carried along. This led to the identification of a large family of genes that control normal cell growth and division. Mutations in these "oncogenes" can transform normal cells into tumor cells, and can lead to cancer.

Pictured lower right: David Baltimore, Ph.D., is president of the California Institute of Technology, a former director of the Whitehead Institute of Biomedical Research at MIT and former president of Rockefeller University. He shared the 1975 Nobel Prize with Howard Temin for identifying reverse transcriptase, and with Renato Dulbecco for other virological research. The discovery of the enzyme opened up the genomes of retroviruses and then all genomes for investigation. It also was the opening salvo in the very successful attack on the nature of cancer that has taken place since 1970, and set the stage for the discovery of HIV.

Retroviruses, engineering and the

FUTURE *of* SCIENCE

A conversation with Harold Varmus and David Baltimore



HAROLD VARMUS, M.D.

ILLUSTRATIONS BY DAVID JOHNSON

Two of the nation's most prominent Nobel laureates discuss recent advances in virology and biomedical research, the role of government and the private sector in the scientific enterprise, and what it will take to continue to make progress in addressing human disease. Should the NIH be reorganized? Is it important to improve the public's "science literacy," and if so, how can that be accomplished?

Editor's note: Baltimore and Varmus were interviewed separately, and their responses were combined in a question-and-answer format.

Where is the field of virology headed?

Varmus: One thing that's happened in the last 20 years that really was unprecedented was the development of drugs that worked to treat viral illness. The idea of using protease inhibitors to counter viral infections had the earliest success with HIV. Now there is reason to believe that people are hot on the trail of developing protease inhibitors for the treatment of hepatitis C. That would be a tremendous advance, because hepatitis C is a virus that is still very difficult to grow.

One of the (other) things we've learned is how to work with viruses that can't even be grown in tissue culture. That seems paradoxical, but we know enough about how to study viral genomes, and pull them apart, so we can understand how parts of them work without having to grow the whole genome.

Baltimore: It occurred to me many years ago that … if you could modify the genetic inheritance of the cell, you could put into the cell something which could in principle totally prevent a virus from growing.

There is not today on the market any such form of "intracellular immunization" against infectious agents (but) in the last couple of years a new method of potentially inhibiting virus growth has appeared, which is called interfering RNAs. They interfere with the growth of a virus in a very potent manner.

So we started to see whether we could adapt this to HIV, by targeting the receptor on the cell. We worked very closely with the laboratory at UCLA run by Irvin Chen. What I call this whole line of work at the moment is "engineering" the immune system. And it raises all the problems that any engineering effort does: How do you make it happen? How do you deliver it? How do you make it safe?

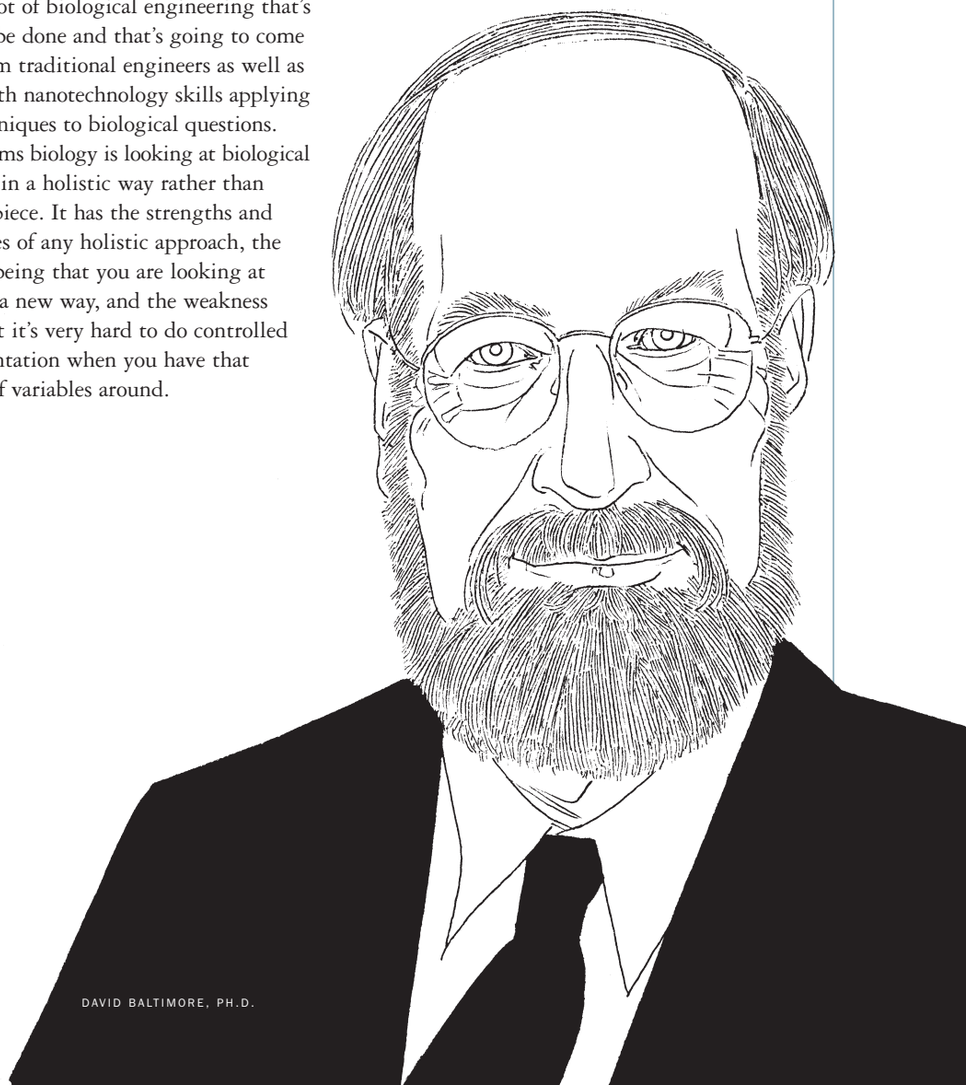
What are some of the forces that will drive biomedical research over the next 20 years?

Baltimore: I think a lot of discovery is going to come from wedding fields that have traditionally been separate. I think there's a lot of biological engineering that's going to be done and that's going to come about from traditional engineers as well as people with nanotechnology skills applying their techniques to biological questions.

Systems biology is looking at biological problems in a holistic way rather than piece by piece. It has the strengths and weaknesses of any holistic approach, the strength being that you are looking at things in a new way, and the weakness being that it's very hard to do controlled experimentation when you have that number of variables around.

But I wouldn't count out traditional modes of carrying out molecular biological research. The human genome was sequenced and turned up lots of genes, the functions of which we know very little about. So there's an awful lot of work to be done just to fill out the catalog. And that's going to turn up some very important and very surprising things.

Varmus: There are incredibly high levels of discovery at the moment. Wherever you turn, the tools are so much more powerful than they were 15 or 20 years ago, thanks



DAVID BALTIMORE, PH.D.

to genomics, computer science and the number of ways in which we can make use of models of disease in a variety of organisms. Just about every field is prospering. I meet with computational people at least once a week and I didn't used to do that. It's because we're using different kinds of tools … that present a density of data that none of us had before. But the basic experimental design is still for the most part unaltered. Sure we use arrays to look at (gene) expression patterns. It broadens our view, but the important work still gets done one gene at a time.

Do you support the NIH "Roadmap," a reorganization of the National Institutes of Health that is being undertaken by NIH Director Elias Zerhouni?

Varmus: Many of the things in the roadmap are the attempt to bring the NIH together to work as a single institution, something which has always been difficult to do, given the way in which the NIH has grown, and the way in which it has been established by Congress as a very large collection of independent units, more like a confederacy than a real union.

There are advantages to confederacy. But the important thing is to recognize when appropriate that every institute at NIH has a stake in common technology development.

One example where I think the work is particularly important is the effort to develop centers for training and research in computational biology, where the issues of multidisciplinary investigation are already very alive. And if Elias is able to keep the team together, despite the fact that the NIH budget is not going to be rising in the years ahead the way it did over the last five years, this would be a big triumph because it's very much needed.

A beautiful problem to study

The battle against HIV actually had its beginnings during the "war on cancer" – years before the first AIDS case was reported.

In the 1960s, scientists were trying to figure out how certain viruses could cause tumors. One result of that research was the discovery of reverse transcriptase, the enzyme that allows RNA viruses to make DNA copies of themselves inside the cells they infect. Viruses that do this are called "retroviruses."

By the time AIDS came along in the early 1980s, scientists were able to test tissues and blood for the presence of reverse transcriptase. The detection of the enzyme was an important clue that the disease was caused by a retrovirus. It led – in 1984 – to the simultaneous discovery of HIV in the laboratories of Robert Gallo and Luc Montagnier.

Since then, AIDS research has accelerated, thanks in part to technologies such as the polymerase chain reaction, which allows rapid identification of genetic sequences.

Other clues are emerging from the study of relatively harmless viruses in laboratory animals. Among the most valuable are reoviruses, a family of RNA viruses that include rotaviruses. In humans, reovirus infection usually does not result in anything more serious than a mild cold or diarrhea, but infection during the first weeks of life – in rare instances – can cause bile duct scarring and resulting destruction of the liver.

Terence Dermody, M.D., who directs the Elizabeth B. Lamb Center for Pediatric Research at Vanderbilt, is an expert on reoviruses. Through their studies, he and his colleagues have gained an appreciation for the remarkable capacity of viruses to "home" to their target cells in the body, to dock in an intricately specific manner to the cell surface, slip into the cell, replicate, and assemble themselves precisely into new packages of infectious material.

Using methods such as X-ray crystallography and cryo-electron microscopy-three-dimensional image reconstruction, by which researchers can visualize frozen viral particles and construct 3-D images of them with the help of a computer, "we can address fundamental structural questions to understand – at an atomic level of resolution – how two proteins interact to create an important biology,'' such as how the virus docks to its target cell, Dermody says.

This information is yielding insights into other, more virulent microbes, such as herpes simplex virus and West Nile virus, which cause encephalitis.

The researchers also are trying to construct potential vaccines for other viruses such as HIV, by introducing HIV genes into the reovirus genome. Because reoviruses are relatively innocuous, extremely stable and trigger strong immune responses, they could be a safe and effective way to vaccinate against their more dangerous cousins.

Unraveling the biology of reoviruses "is a fascinating problem … a beautiful problem to study," Dermody says. "It keeps us up at night."

Cancer-causing viruses also are an important research avenue. "Fifteen to 20 percent of all human malignancies have a viral etiology. That's not a trivial amount," says Philip Browning, M.D., an expert on cancer viruses at Vanderbilt. "If we had vaccines for those viruses, then we could potentially prevent these tumors."

For example, vaccines have been developed to prevent infection by the hepatitis B virus, which can cause liver cancer, and infection by the human papilloma virus (HPV), which causes half of all cervical cancer.

Studies of cancer-causing viruses in the 1960s and 1970s laid the groundwork for understanding how cancer develops. Oncogenic viruses can produce tumors by blocking genes and proteins that control normal cell growth and division. Mutations in these genes also can trigger abnormal cell growth – even in the absence of viral infection.

"Viruses are always better cell biologists than we are," Dermody explains. "So if we can hitch a ride on a virus and figure out how it gets into a cell and how it replicates, we're going to learn a lot about how cells work."

Basic research is key to preparing for the next pandemic, as well. "Scientists need to be equipped with all the skills to address these questions when the next HIV or SARS coronavirus comes," Dermody says. "Nobody can tell what the next virus is going to look like … Tomorrow the whole world may be tipped on its ear."

– BILL SNYDER

Baltimore: I believe that what Dr. Zerhouni is saying is that research has reached a new level of sophistication that we haven't seen before, and that at this level of sophistication, we have to be able to think more strategically than we have in the past. And I happen to think he's right about that.

It involves us in doing things in new ways, and as such is a little scary. I think it's good to be experimental. It's a measure of the success of the biomedical enterprise that we can start thinking in new ways, and we should be excited by that kind of success, rather than saying, "All we need is more of the same."

How is the Grand Challenges in Global Health, a $200 million initiative supported by the Bill & Melinda Gates Foundation, adding to the nation's research enterprise?

Varmus (who chairs the initiative's executive committee and scientific board): I do believe that the NIH has a major responsibility to address diseases throughout the world, not just diseases that are prevalent in the U.S. (But) I certainly don't believe that NIH should be funding all the research that gets done. There are lots of other outstanding sources of funding for research … and these other sources ought to be applauded and sustained.

The real appeal of the Grand Challenges comes from its unique aspects; that is, trying to focus on what we as a scientific board thought to be obstacles (to) making much more rapid progress in confronting diseases in developing countries. The initial request for ideas resulted in our receiving over 1,000 proposals from well over 70 countries. We won't know for several years whether this really works, but every step so far has been very successful.

How well are we training the next generation of scientists?

Baltimore: We're doing a good job in training; the problem is, we don't have enough people. In particular, the number of engineers and physical scientists who are being trained is just simply too small.

What we've been doing is using immigrants in the place of training our own people, and that's worked perfectly well. We have large numbers of immigrants coming in continually from countries where they are training people in engineering and science, and those people play a central role in the biomedical enterprise and the general research enterprise in the United States.

Varmus: I have concerns about the way in which we're training people. One of those concerns is the need to learn computation at the same time that one learns biology. This is something that can only be rectified by new curricula for undergraduates, by generating centers in which people who are trained in computation or statistics or computer science are side by side with biologists training students to know both languages.

What attracted you to a career in science?

Baltimore: First of all, I found it easy, and so I followed my nose. My mother (Gertrude Baltimore) was a scientist, and nudged me at critical times in my life into directions that were very powerful and very effective.

She studied experimental psychology with the Gestalt psychologists at the New School for Social Research. She taught at the New School for many years, and then went to Sarah Lawrence College where she taught for the rest of her career. She was a great teacher, and anybody I've every run into who was touched by her at Sarah Lawrence told me how special she was.

Varmus: I spent most of my college career running away from science. I did the premed requirements, but one of the things that was most important to me when I was at college was my work as an English major studying Charles Dickens … Then I went to graduate school in literature for a while before going back into medicine.

I was not particularly interested in putting on a uniform and going to Vietnam ... Because I was a reasonable student at medical school, it wasn't all that difficult for me to get into a government program that would allow me to do research, in this case at the NIH. I ended up, despite an almost complete lack of research experience, in the laboratory of Ira Pastan. He was a terrific mentor, and got me excited about molecular biology. The serendipity factor for most people has a lot to do with who you run into and how they influence you.

Why did you get involved in administration?

Varmus: I never saw the NIH as an administrative job. What I found interesting were the policy issues. What is the direction medical research should be taking? How do we show the public the best side of science? How do we advertise our science? I saw this as a chance to do public service.

Baltimore: I discovered long ago about myself that I am interested in the institutions that make science happen. A very important part of the scientific enterprise is the maintenance of strong institutions, because all science takes place in institutions. That's where all the money goes.

I never thought that I would do anything about this interest until I was offered the opportunity to start the Whitehead Institute (in 1982). I found it extremely rewarding to do that. But at the same time, I haven't wanted to leave behind my science, and so I managed … to continue to run a large laboratory.

How do we encourage more young people to go into the sciences?

Baltimore: We need more mothers like my mother! I really don't know the answer because it involves our whole society, the way it functions and what it honors. Developing the capabilities to be a scientist is very hard, because it involves learning a lot of mathematics and science, generally when you're very young.

We don't have a society that honors people who work hard. We have a society that honors people who play hard, that is great athletes or great entertainers. But the people who are really driving our society are anonymous. They are the scientists and engineers who are making the discoveries and devising the gadgets that make our lives easier and better.

Varmus: For our society probably a more fundamental issue is: how do we make citizens who are more capable of thinking in an evidence-based way? That actually is one of the biggest problems we face as a country, that we don't teach people to do that, yet we could.

We could be giving virtually all of our instruction in grade school in a way that emphasizes experiment (and) observation … as opposed to rote and ritual. We'd have a more informed electorate. An awful lot of political issues these days are based on questions that have a scientific component.

LENS

Pictured left, above: Young people congregate in front of the graffiti-splashed wall of the GHESKIO center across the street from one of the poorest slums in Port-au-Prince, Haiti.

Below: GHESKIO patient Edner Hyppolite raises his arms in thanks for the medication he is receiving to control his HIV infection.

Photography by Jonathan Rodgers

"It's not impossible at all"

Bringing AIDS therapies, vaccine trials to the poorest nation in the Western Hemisphere

By Bill Snyder

Across Harry Truman Boulevard from one of the poorest slums in Port-au-Prince, a corps of dedicated health care professionals is slowly, stubbornly mastering one of the worst scourges in the history of humankind.

Beset by frequent political turmoil, Haiti is the poorest nation in the Western Hemisphere. It also has the highest rate of HIV infection on this side of the globe. Yet Haiti's AIDS burden has never come close to the levels seen in some West African nations, and it seems to be declining.

"To me this is the most amazing thing. If you can do it here in this chaos, we know it can be done everywhere," says pioneering Haitian physician Jean Pape, founder and director of the GHESKIO centers, the oldest AIDS research organization in the developing world.

By documenting HIV-tainted blood transfusions, GHESKIO convinced the Haitian Ministry of Health – its constant partner and supporter – to replace commercial blood banks with Red Cross blood centers. Encouraged by public education campaigns, condom sales have risen, and the HIV infection rate has been cut in half – to about 3 percent – since the mid-1980s.

GHESKIO is an acronym that – in French – stands for the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections. Since it was established in 1982, GHESKIO has received support from the National Institutes of Health and assistance from New York's Weill Cornell Medical College, where Pape is professor of International Medicine and Infectious Diseases.

In the early 1990s, GHESKIO began a new relationship with Peter Wright, M.D., chief of the Pediatric Infectious Diseases division at Vanderbilt University Medical Center. Cornell and Vanderbilt provide medical expertise and help train Haitian physicians, and young U.S. physicians gain experience at GHESKIO treating HIV and other illnesses.

GHESKIO logs more than 100,000 patient visits a year for free testing, counseling and treatment. Thanks to lower-cost generic drugs, the group was able to provide combination anti-retroviral therapy for the first time last year. So far, 2,000 patients have been treated. That's a drop in the bucket compared to the estimated 400,000 people who are infected in this Caribbean nation of 8 million.

"Now the challenge is how to implement anti-retroviral therapy across the country, when the health infrastructure is very poor and sometimes very unreliable," says Vladimir Berthaud, M.D., a native Haitian who directs the Infectious Disease division at Meharry Medical College in Nashville. "There are a lot of logistical problems. But it's not impossible at all."

Toward that end, Berthaud and his physician colleagues at Vanderbilt – David Haas and Catherine McGowan – are helping to establish an International AIDS Clinical Trial Unit in Port-au-Prince. "You have to be able to measure what you're doing," Wright explains. "Without a lot of training of physicians and education of the people, it won't make sense to just spread out some anti-retroviral drugs."

Over the years, GHESKIO has fostered a strong sense of trust and loyalty among Port-au-Prince residents, many of whom live in tin-roofed shacks without plumbing or electricity. GHESKIO patients are enrolling in clinical trials, and healthy subjects are signing up for tests of a candidate HIV vaccine.

Continued support from the United States is crucial, Pape says. Adds GHESKIO patient Nicole Marcelin: "Remember what is on the dollar bill – 'In God We Trust.' It means (Americans) … will help people who are living with the virus. When they help them, they also help themselves." **LENS**

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Bringing together leading scientists in a relaxed atmosphere to present and discuss cutting-edge research that will shape the future of the biological and biomedical sciences.

May 23-26
Frontiers in addiction biology: Genomics and beyond

Keynote speaker – **Paul Greengard**, Ph.D., Vincent Astor Professor of Molecular and Cellular Neurosciences, The Rockefeller University, New York; 2000 Nobel laureate for discovering how dopamine and other transmitters exert their actions in the nervous system.

Topics include:
Genetics of alcoholism, opiate and cocaine addiction; A molecular switch for addiction; Mass spectrometry based imaging of psycho-active drug action

June 6-9
Frontiers in genome engineering: Building a better mouse

Keynote speaker – **Allan Bradley**, Ph.D., Director, The Welcome Trust Sanger Institute, Cambridge, England; pioneer in the use of embryonic stem cells and "knockout" mice to engineer the mouse genome.

Topics include:
Embryonic stem cells – a shortcut for functional genomics in the mouse; Manipulation of organogenesis *in utero*; Tools for analysis of murine gene function

June 16-18
Mathematical models in signaling systems

Keynote speaker – **Leroy Hood**, M.D., Ph.D., President, Institute for Systems Biology, Seattle; pioneer in protein and DNA sequence and synthesis technology; Lasker Award winner for detailing in molecular terms the genetics of antibody diversity.

Topics include:
A mechanistic model of a complex signaling pathway: impact on drug discovery; Towards a molecular spectrometer of the cell; Networks of connections within proteins

June 20-23
Pharmacogenomics: From concept to clinical practice

Keynote speaker – **William E. Evans**, Pharm.D., Scientific Director, St. Jude Children's Research Hospital, Memphis; Nationally known expert on the pharmacogenomics of cancer chemotherapy and childhood acute lymphoblastic leukemia.

Topics include:
Analysis of complex traits; "Race" and drug prescribing; Pharmacogenomics of asthma, cancer and depression

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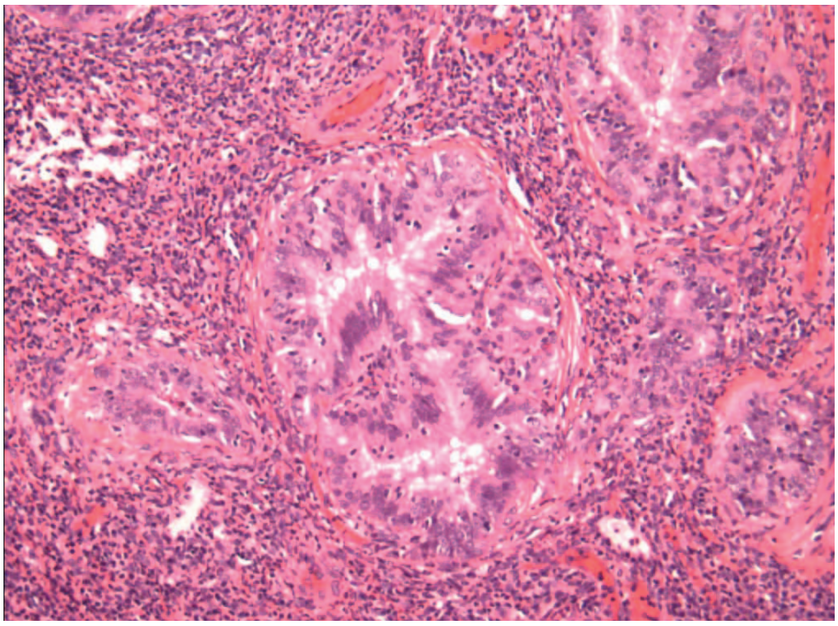
Histology preparation shows gastric cancer arising from an inflammatory stomach lesion, which in turn resulted from infection by the *Helicobacter pylori* bacterium. *H. pylori* infection is a major cause of stomach ulcers and gastric cancer in humans.

Image courtesy of M. Kay Washington, M.D., Ph.D., professor of Pathology, Vanderbilt University Medical Center



IN THE NEXT ISSUE:

The inflamed heart
Cholesterol is not the only culprit in heart disease; chronic inflammation also may play an important role.

Nurturing the tumor
Inflammatory cells and proteins may promote cancer growth and aid its spread to other parts of the body.

The changing paradigm
From the outside to the center of the cell, signaling pathways underlie the deleterious effects of inflammation.

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