

SABIN VACCINE REPORT

the newsletter of the Albert B. Sabin Vaccine Institute at Georgetown University

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Gates donates \$100 million for children's vaccines

BY JOHN CLYMER AND DIANE MYERS

Microsoft billionaires Bill and Melinda Gates have made a \$100 million gift to establish a program to accelerate access to new vaccines for children in developing nations. The goal of the Bill and Melinda Gates Children's Vaccine Program is to significantly reduce the time it currently takes for vaccines to reach children living in poor countries.

The initiative is a program of the William H. Gates Foundation and will be administered by the Program for Appropriate Technology in Health (PATH). Headquartered in Seattle, PATH will work with the World Health Organization, UNICEF, the World Bank, the Children's Vaccine Initiative, vaccine manufacturers, governments and nongovernmental organizations.

PATH plans to focus on four recently developed or about-to-be-marketed vaccines against respiratory, intestinal and liver diseases. Global use of the vaccines could reduce childhood deaths by 33%, representing 2.5 million lives, and reduce liver cancer deaths by 75%. Two of the vaccines prevent respiratory ailments caused by the bacteria *Haemophilus influenzae* type b, or Hib, and *Streptococcus pneumoniae*; a third prevents rotavirus infection, which causes severe diarrhea, and the fourth vaccine being considered prevents hepatitis B, a viral liver disease.

In the United States, vaccines for Hib and hepatitis B are part of the recommended childhood immunization schedule, and vaccines for rotavirus and *Streptococcus pneumoniae* are expected to become part of the recommended immunization schedule soon.



Phillip Russell (l), Suryanarayan Ramachandran, and James Maynard.

Decreasing the "lag time"

Why is the Gates Foundation program of such importance? New, life-saving vaccines generally are in broad use in industrialized countries several years before they become widely used in developing countries where the need is greatest. This time lag in vaccine "uptake" is due to economic, logistical and other challenges.

"We have a social imperative to work together to address this basic inequity," said Bill Gates, trustee of the

William H. Gates Foundation. Sabin Vaccine Institute chairman H. R. "Shep" Shepherd applauded Gates' vision and the establishment of the Children's Vaccine Program. "Vaccines are the most powerful tool available to equalize the health of human beings in every corner of the world," he said. "Enlightened leaders understand the power of vaccines to help bring peace and opportunity to the most troubled places in our world. Vaccines are the microchip that will revolutionize healthcare," Shepherd declared.

The Children's Vaccine Program will specifically support ways to make the vaccines widely available to children in developing countries. It will not be used to buy the vaccines.

The program will be managed by a Secretariat based at PATH, under the guidance of a Strategic Advisory Council that is composed of seven international experts in vaccinology and vaccine introduction. Philip K. Russell, founding president of the Albert B. Sabin Vaccine Institute, is a member of the Strategic Advisory Council. He lauds the Gates' program as a "very exciting development in the field of international health."

An "entrepreneurial" approach

According to Russell, who has years of experience *continued on page 7*

Rotavirus vaccine could benefit 500 million children

BY RACHEL LIBERATORE

Although rotavirus infections affect 300-500 million children every year, this disease has only recently provoked the kind of intense research investment one might expect for such a ubiquitous affliction. Unfortunately, the reason for this is the same for many diseases whose primary targets are nations in which the average per capita health expenditure hovers just around \$10. In the case of rotaviruses, this trend of apathy toward diseases in developing nations was turned around following studies demonstrating that this disease actually leads to a significant amount of health care expenditure in developed countries, where the ability to pay for preventive and prophylactic treatments is much greater. Once a lucrative market was established, a vaccine for rotavirus was soon developed and has been recently licensed.

Rotaviruses are the infectious agents responsible for most cases of childhood diarrhea. Ninety-five percent of children worldwide are exposed to rotaviruses between the ages of three and five, though in developing nations initial exposure is usually within the first year of life. Such intestinal infections are particularly dangerous in children because they are more likely than adults to suffer from dehydration, especially if they have previously compromised health.

In August 1998, the Food and Drug Administration (FDA) approved the first rotavirus vaccine since the discovery of rotaviruses in 1973. The vaccine, called RotaShield™, was developed by Albert Z. Kapikian of the Laboratory of Infectious Diseases (LID) at the National Institute of Allergy and Infectious Diseases (NIAID) along with other colleagues at the National Institutes of Health. The vaccine is manufactured by Wyeth-Ayerst Laboratories at a cost of approximately \$38 per dose.

Ideally, a vaccine is supposed to save society money because the price of the vaccine is less than the cost of treating the disease. From the perspective of the health care system, however, the cost of the vaccine should be high enough that the system does not lose money due to the decreased need for treatment. A study headed by Roger I. Glass, chief of the Viral Gastroenteritis Section at the Centers for Disease Control and Prevention (CDC), determined that a rotavirus vaccine would be cost-effective to both society and the health care system in the United States if the cost fell within a range of \$9-\$51 per dose. Glass's pivotal study is widely credited with providing the impetus for the pharmaceutical industry to devote resources to rotavirus vaccine development, which ultimately led to the approval of RotaShield™.

According to Glass, although "there is a clear need for rotavirus vaccine for all children, without the demand and money of the developed countries, it is unlikely that any country would be interested." As evidence, he points to the failures of new cholera and typhoid vaccines, needed in developing countries but now priced and sold for travelers—a tiny and nonviable market.



Roger Glass

photo by Erica Seiguer

continued on page 7

Controlling Malaria Will Require an International Effort

BY HOWARD ENGERS, PhD

Malaria alone accounts for over 2% of the total global disease burden and five times this figure in Africa, ranking third among major infectious disease threats. There are an estimated 300-500 million cases of malaria each year, resulting in over 1 million deaths, mainly of children under five years old in Africa. Augmented by the more recent impact of globalization, the disease is often linked to poverty, the movement of refugees or populations seeking work and to environmental change, including forestry, mining and water development projects.

We can conquer malaria. But to do so, will require a concerted global effort, involving Private and Public sector participation and that of civil society. All manner of resources will need to be brought to bear. Better ways must be found to apply existing control methods. Improved tools must be developed and solutions need to be identified to circumvent and combat emerging problems including social/political unrest, the widespread resistance of the malaria parasite to existing drugs and the potential change in the distribution and incidence of malaria due to anthropogenic climate change.

Reflecting its prominent status as a global killer, malaria has been a priority for World Health Organization (WHO) since its founding in 1948. A revised WHO Global Malaria Control Strategy was adopted at the Amsterdam Summit of 1992, based on a renewed global commitment to malaria control. Recognizing the widespread political desire that has been building over this decade, the new Director General of WHO, Dr G.H. Brundtland, declared upon taking office in July 1998 that there should be a deeper commitment to win the fight against malaria. Greater financial resources and a higher visibility for malaria control activities would be necessary. This declaration led four UN-System agencies (UNDP, UNICEF, WHO and the World Bank) to launch Roll Back Malaria (RBM) on 30 October 1998. The RBM project, co-ordinated by WHO, aims to: 1) support governments and partners; 2) improve technical efficiency and capacity, including the development of new methods, new tools and capacity strengthening in the malaria endemic countries; 3) to improve resource allocation, utilization and mobilization.

The development of an effective malaria vaccine represents one of the most important strategies for providing a new, cost-effective tool to be added to the currently available armamentarium of malaria control interventions. Its effectiveness will depend on having a sound and adaptable delivery structure. An affordable malaria vaccine which could be implemented through the existing Expanded Programme on Immunization (EPI) and which would reduce overall childhood mortality by 20-30% or more, with a duration of immunity of three years or more, would represent a very powerful intervention strategy. However, as no single intervention tool is likely to represent a panacea for malaria, an effective vaccine would be applied together with other appropriate cost-effective methods.

Over the past decade, there has been significant progress in the identification of vaccine candidate antigens and their genes. However, due to the complexity and cost of vaccine development and the relative lack of commercial interest, only recently have the leading candidates started to enter clinical and field trials. At least three are now under clinical trial and several additional candidates are in the development pipeline. Despite the fact that no acceptable vaccine has emerged to date from the many field trials conducted, scientists have made major progress in conceptual thinking and in the design of the trials required for the evaluation of candidate malaria vaccines. Recent advances in research technology, including the availability of synthetic antigens, DNA vaccines, malaria parasite genome sequences, functional genomics and novel adjuvants have led to an acceleration in the rate of progress. The hope, and increasingly the expectation, is that this will herald a new era of malaria vaccine development.

In order to capitalize on this technological progress, sustained political commitment and investment in malaria vaccine development will be essential. Such investment has a high probability of success and is likely to pay dividends in the form of new, highly effective tools for use in improving the control of malaria at the global level. In addition to the new RBM project, several public-private sector initiatives which were established recently, including the Multilateral Initiative for Malaria in Africa (MIM) and the New Medicines for Malaria Venture (MMV), provide renewed hope that these institutions and agencies can work together to agree upon, establish and implement a common global strategy for the development and clinical testing of leading malaria vaccine candidates over the next five to ten years. The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) is fully committed to the promotion and implementation of such a global strategy, in collaboration with its Public and Private sector collaborators. Partnerships will have to be forged or strengthened at the national and international levels to ensure that fundamental infrastructures, and production and delivery systems are in place.

Provided that scientists, malaria control programs and donor agencies succeed in working better together worldwide, the next decade will certainly bring many significant advances in the quest to develop and implement an effective, affordable malaria vaccine—allowing people to be free from a life of disease and misery, hopefully sooner rather than later. ❖

Howard D. Engers has been with the World Health Organization since 1987. Engers has a record of achievement internationally as a scientist, educator and manager in the academic community, national research institutes and international agencies. From 1991-1999, he has held the position of manager, Steering Committee on Vaccines for Malaria, and Malaria Research Coordinator, Special Programme for Research and Training in Tropical Diseases (TDR).

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*A scientist who is also a human being cannot rest while
knowledge which might be used to reduce suffering sits on
the shelf.*
Albert B. Sabin

The Albert B. Sabin Vaccine Institute is a non-profit
institute dedicated to continuing the work and achieving
the vision of Albert B. Sabin: to fully realize the potential
of vaccination to prevent disease.

Founded in 1994, the Institute strives to prevent
disease by promoting the
development of new vaccines and delivery systems.

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Editor's Note:
As I will be leaving the Sabin Vaccine Institute in June to begin medical school, I leave the *Sabin Vaccine Report* in the capable hands of the new Editor, Charlene A. Flash. The *Sabin Vaccine Report* will continue to bring you interesting, thorough coverage of the latest in vaccine research, development and public policy. I wish Charlene and the staff the best of luck.

Quantifying the global burden of malaria remains difficult but essential

BY SEAN C. MURPHY AND JOEL G. BREMAN, MD, DTPH

The worldwide burden of malaria is difficult to precisely quantify because current morbidity and mortality estimates are variable and imprecise. Despite these inadequacies, the World Health Organization (WHO) and other groups suggest that up to 500 million clinical cases of acute malaria occur globally each year, primarily in Africa (1). The lack of precise estimates is due to the protean clinical manifestations of the disease and poor surveillance worldwide. Among those who contract malaria, it is estimated that about 1.5-2.7 million die annually. In Africa, most deaths are not reported by health authorities because of inadequate health care delivery systems and because malaria commonly occurs in rural settings; 1.0-1.9 million African deaths have been estimated yearly since Bruce-Chwatt's first study in 1952 (2,3). In addition, malaria morbidity weighs very heavily on Africa's fragmented health programs — a large percentage of hospital admissions and patient visits to dispensaries are malaria-related. In all endemic areas, malaria also has important economic implications resulting from decreased productivity of infected individuals and their care-givers.

Despite the inadequacies in surveillance, there is a consensus that 90% of malaria cases and deaths occur in Africa, where *Plasmodium falciparum* and *Anopheles gambiae* predominate and the greatest toll is in children less than five years of age. The widely variable data do not sufficiently account for the impact of malaria during pregnancy, on childhood anemia, and as a cause of neurologic and developmental disorders. Malaria epidemiology markedly varies in different areas and is rarely considered in regional or global calculations. Increasing resistance of *Plasmodium falciparum* to drugs and *Anopheles* mosquitoes to insecticides will undoubtedly worsen the malaria situation worldwide.

Recently, national governments, WHO, and other international health agencies have shown greatly renewed interest in malaria. These partners are interested in research, control, and prevention, and are aware of the importance of carefully measuring the impact of new and improved interventions (including vaccines) on malaria-endemic populations. To aid these efforts, an attempt to define more accurately the range of malaria-related morbidity and mortality is being undertaken. A review of clinical and epidemiologic reports indicates that acute febrile illness, with or without parasitologic confirmation, has been the basis of reporting to national officials and WHO. Thus there are several important malaria-associated conditions and several host factors that are generally not considered in national and international studies.

Malaria in pregnancy

Malaria plays an important role in newborn survival, through pregnancy-related complications such as abortion, stillbirth, and low birth weight (LBW £2500 g). In 1985, it was reported that LBW was the most important predictor of neonatal and infant mortality, and a major cause of newborn neurologic disorders (4). The relative frequencies of these pregnancy outcomes have not been fully quantified, although LBW and its consequences are the most frequent pregnancy-associated complications of malaria, particularly in Africa, where up to 17% of all live births and 34% of first-born infants have LBW. LBW has been highly correlated to placental malarial infection, which is linked to maternal parasitemia (5).

Malaria and neurological disorders

Neurologic sequelae following cerebral malaria have been recognized for over 50 years. Complications

can include persistent cortical blindness, deafness, severe cerebral palsy, hemiplegia, and other less extreme symptoms. A small percentage of all malaria cases and up to 12% of cerebral patients experience these disorders. Most of these problems appear to resolve within six months in properly treated patients, however, up to 25% of these disorders result in permanent disability (6). A large percentage of these patients is severely ill and does not receive comprehensive medical care and rehabilitation services. The long-term impact of severe and milder forms of malaria on these complications, including learning and behavioral disabilities, is not known or fully appreciated.

Malarial anemia

Malaria-induced anemia results in substantial morbidity and mortality and is accelerating with parasite resistance to drugs. Hospital records in Africa show that anemia in children is increasing. Malaria is a major cause of anemia-associated hospital admission, and very low hemoglobin (£5gm%) is associated with death within a short time of admission (7). The precise interrelationship and impact of malaria on anemia and its clinical manifestations have not been addressed fully.

Host factors

Studies in the 1960s showed that sickle cell trait confers some protection against death from falciparum malaria and that Duffy blood group antigen must be present on red blood cells to allow vivax malaria to enter. These observations, coupled with recently reported associations between malaria and ma-

JOR histocompatibility complexes, suggest that genetic factors play an important role in the clinical and epidemiologic manifestations of malaria. The role of host factors on morbidity and mortality remain to be defined.

What next?

Research efforts in drug discovery, vector control, and vaccine development will yield interventions in the 21st century that will ultimately reduce substantial malaria morbidity, mortality and economic loss. Precise estimates and increased knowledge of the toll of malaria are needed urgently to assess the current status of the disease, to monitor the progress of prevention and control programs, and to measure the success of new and improved anti-malarial drugs, vector control agents, and vaccines. ❖

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Malaria on the Web

The following websites provide information on malaria. The Sabin Vaccine Institute does not assume responsibility for the information contained in these sites.

The Malaria Foundation International

www.malaria.org

Malaria Research at the National Institutes of Health

www.niaid.nih.gov/dmid/panel.htm

WHO Research and Training in Tropical Diseases

www.who.int/tdr

Multilateral Initiative on Malaria at the Wellcome Trust

www.wellcome.ac.uk/mim

Rotarians Against Malaria

www.bednet.org/

Malaria information at the Sabin Vaccine Institute

www.sabin.georgetown.edu

When preparing for travel, consider malaria

The most common imported disease can humble the unprepared traveler.

BY CHARLENE A. FLASH

Before the *Hot Zone* brought the Ebola virus into the public eye, and before HIV became a household term, malaria was the exotic disease of the 20th century. Although malaria is considered by some to be a disease of the tropics, relegated to the developing world, mosquitoes carrying malaria have been found in various regions of the United States as well as many non-rural areas in third world countries.

Malaria kills 1.5-2.7 million each year and is the most common imported disease. Malaria is caused by the *Plasmodium* parasite and is spread by the bite of the *Anopheles* mosquito, which serves as the parasite's vector. Vector-borne diseases travel very quickly with an exponential infection rate. According to the CDC, malaria may lie dormant in an infected individual for as much as year and then will show symptoms such as fever, chills, muscle aches, headache, nausea, vomiting and diarrhea, which may not necessarily be immediately recognized as malaria by physicians.

Protection must begin with your immediate surroundings. Bug sprays, netting and clothing which covers most of the body can protect people from getting bitten by the mosquito. Bed netting is indispensable because mosquitoes are very active during the evening hours. Pyrethum is an insect repellent which when sprayed in the air is effective

against the bites of flying insects. It is effective on clothing for up to 3 weeks after initial application. DEET (N,N-diethylmetatoluamide) is considered to be the most effective insect repellent for use on exposed skin.

Antimalarial medications should be taken two weeks prior to travel. Aralen, a medication con-

Although malaria is considered to be a disease of the tropics, relegated to the developing world, mosquitoes carrying malaria have been found in various regions of the U.S.

taining chloroquine phosphate should be taken a week or two prior to departure and for four weeks following return. Other related medications include Lariam, a medication containing mefloquine doxycycline and Mefloquine. Many travelers neglect to take their malaria pills, leading to preventable fatalities.

Be sure to consult the appropriate travel health professional or inform your physician that you have been travelling in a region where Malaria is prevalent. Different geographical locations have different strains of malaria characterized by varying levels of resistance to anti-malarial drugs. A travel health professional can advise you as to the appropriate anti-malarial drugs to take and the schedule of administration. ❖

Sean C. Murphy (smurfdog@iastate.edu) is a junior at Iowa State University. He was an intern at the Fogarty International Center (FIC), National Institutes of Health (NIH) during the summer of 1998, where he studied the impact of malaria on populations, particularly those in Africa. Joel G. Breman, MD, DTPH is Deputy Director of the Division of International Training and Research, FIC, NIH.

History of malaria control and vaccine development highlights s

BY ERICA SEIGUER

Out of sight, out of mind, the old adage goes. Nothing could be closer to the truth for malaria, a disease which, it can be convincingly argued, is to blame for crippling health and economies all over the world—especially those of developing countries. Despite the demonstrable impact of malaria, research and development of treatments and prophylactic strategies have been neglected, most probably due to the fact that malaria is primarily a disease of the developing world and is of little perceived threat to the developed world where most biomedical research is conducted. Roughly 40% of the entire world's population is at risk for becoming infected.

Malaria is a crafty parasite, and has developed resistance to virtually every agent man has devised in at-

tempts to humble it. It also takes on many forms within its human hosts, tricking the immune system with every morphological switch. Its biological savoir-faire has made chemotherapeutic and prophylactic agents elusive. Drugs that once seemed to spell the end of malaria have failed because of the emergence of resistant parasites. A successful vaccine could

save millions of lives and have a major positive impact on the global economy; a 1991 study by DS Shepard et al., of the economic impact of malaria in Africa found that malaria costs more than \$1.7 billion per year in medical care and lost productivity. For economies struggling to survive in the global market, the impact of malaria and other major diseases create seemingly indomitable obstacles to prosperity.

According to a 1996 report by the Unit for Policy Research in Science and Medicine (PRISM) at the Wellcome Trust, support for malaria research has fallen recently. In their audit of international activity in malaria research, PRISM concluded that

Despite the extent and severity of the condition, as well as the proven value of research for practical health gain, global expenditure for malaria research is very low. Total identifiable worldwide spend was approximately US\$84 million in 1993, representing a research investment for each malaria-related death of approximately US\$42. This figure compares very poorly with available data indicating that research expenditure per death may be orders of magnitude higher for conditions such as cancer, HIV/AIDS or asthma. (p.73)

Perhaps the lack of investment of malaria is a reflection of the United States' tendency towards isolationism; malaria has been classified *de facto* as a disease of the developing world, and not of great concern to the West. It is clear upon inspection, however, that malaria is of great importance to developed countries. And, as Breman and Murphy describe in an accompanying article, the worldwide burden of malaria extends far beyond the actual 500 million annual cases of malaria and the 1.5 to 3 million deaths the World Health Organization (WHO) blames on the disease.

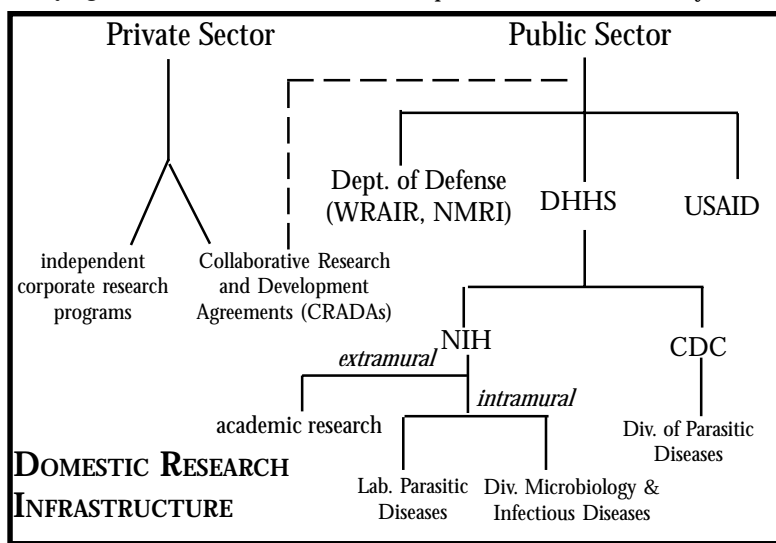
A neglected disease

Malaria is, in many respects, a neglected disease. Why? *Because it is a disease of the developing world.* Beyond the formidable scientific challenges posed by the wily parasite, malaria's victims are for the most part the poorest of the poor in the world. The fact that they could never pay western prices for a vaccine gives the private sector little incentive to invest millions of research and development dollars. Furthermore, vaccines have traditionally been neglected in terms of research dollar investment. This is despite the fact that vaccines are the most humane and cost-

Erica Seiguer, a research fellow at the Institute, graduated in 1998 from Princeton University with a degree in molecular biology and a certificate from the Woodrow Wilson School of Public and International Affairs.

effective health intervention known to man. Much like HIV vaccine research, which has been plagued by meager investment and a decline in the number of companies that maintain HIV vaccine research programs, malaria vaccine research has been passed over by industry and generally left to the public sector.

Malaria, in concert with HIV and tuberculosis, form a kind of oppressive junta that is devastating the world's poor. The combined efforts of malaria, HIV and tuberculosis, if not reigned in, could profoundly stunt economic and health development and jeopardize global financial prosperity. Worldwide, malaria is responsible for the deaths of 3000 children every day—a higher mortality rate than the more visible and more studied HIV. In Western industrialized nations, however, malaria, like many tropical diseases, is a curiosity and not a major concern to



the general public. Most Americans are probably not aware that malaria was a major cause of morbidity in the Civil War, when 80% of the Black soldiers in the Union army got malaria annually. Moreover, data from the early part of this century shows that there were more than half a million cases of malaria in the

An old plague

Malaria is by no means new to humankind. Since the beginning of the written word, about 6000-5500 BC, there have been references to a disease marked by deadly fevers which experts believe were malarial in root. Hippocrates wrote about malaria 2500 years ago—he linked malaria transmission with pools of still water. It was not until 1882, however, that the transmission of malaria by mosquito was hypothesized; this theory was proven by English scientist Ronald Ross at the turn of the century. He was awarded the Nobel Prize for Physiology or Medicine in 1902 in recognition of his seminal work.

Treatment and control of malaria has a long, if ultimately unsuccessful, history. Quinine, derived from the bark of the Cinchona tree, has been used since the 1600s to treat malaria. Chloroquine was developed in 1943, but by the 1960s and 1970s, resistance had been established in Asia and South America. By the 1980s, resistance had spread to most of Africa.

At the turn of the century, vector control, or the targeting of the mosquito as the carrier of malaria, was a popular intervention with the United States Military. From 1904-1906, the U.S. military worked to drain swamps in the Panama Canal Zone and in the 1930s and 1940s, the U.S. government through the Works Progress Administration engineered the draining of swamps throughout the southern regions of the U.S.. The Public Health Service funded more malaria control programs in the late 1940s. The arrival of insecticides like DDT was instrumental in turning the tide against malaria. The result of the various malaria control efforts was the declaration in 1953 that the U.S. was malaria-free. That is not the case today. In the United States there are at least 1000 documented cases of malaria each year.

The 1950s saw a world increasingly optimistic of the possibility of global eradication, most of this hopefulness a result of the use of the insecticide DDT to kill the Anopheles mosquito, the carrier of malaria. Ten years after the beginning of the global *eradication* campaign, the goal was scrapped and malaria *control* became the new aim of international efforts. The United States, through the U.S. Agency for International Development (USAID), contributed \$790 million for the initial eradication campaign from 1959-1969, and a total of \$1 billion from 1955-1970 to the WHO and other agencies for eradication efforts.

Reading the literature of malaria research, the impact of malaria is striking. Malaria is a humbling scourge; despite its co-habitation with humans for thousands of years

it has remained an indomitable foe. In May 1969, the Walter Reed Army Institute of Research (WRAIR) convened a panel workshop on malaria. At that meeting, Major General Joe Blumberg, the Commanding General of United States Army Medical Research and Development, reflected on the challenges posed by malaria and the efforts of the military to control the disease. "I have come to realize that the U.S. Army carries the brunt of this program for the free world," he said. "No other concerted effort is being made since in the United States malaria is not a public health problem. However, when our military are called upon to serve out of the United States, in areas where malaria exists, it becomes an important problem."

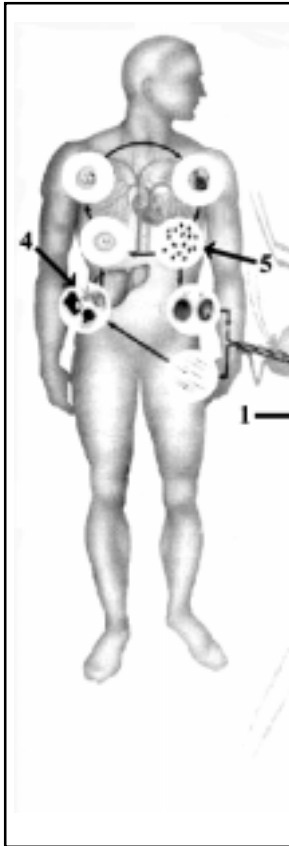
The impact of malaria on the ability of the military to protect U.S. interests in endemic regions has been quite dramatic. In the year 1968 alone, for example, U.S. military forces in Vietnam documented 12,000 cases of malaria, resulting in 250,000 man-days lost. Clearly, malaria poses a major threat to the success of military interventions. Perhaps it is no surprise then that it is the military that has consistently maintained its malaria research program, despite the fact that malaria is a rare occurrence in the United States.

Today, the USAID remains committed to the development of a vaccine for malaria and other approaches to lessen the burden of the disease in developing nations. As an integral component of the *ad hoc* Federal Malaria Vaccine Coordinating Committee (FMVCC), which includes representatives from the National Institutes of Health, the Centers for Disease Control, the Walter Reed Army Institute of Research (WRAIR) and the Naval Medical Research Center (NMRC), USAID has worked to improve coordination and cooperation among researchers. According to Carter Diggs, a Senior Technical Advisor for the Malaria Vaccine Development Program (MVDP) at USAID, this is a tall order. "Scientific culture rewards individual creativity, thus fostering competition and the perceived need for secrecy regarding scientific discoveries, at least until first publication. Program managers' objectives and responsibilities are institutional, not global, preventing pooling of resources to advance the common good."

There is no easy solution to the political nature of the scientific enterprise, posits Diggs. "FMVCC has not transcended these forces that impede coordination and cooperation," he says. "But in practical terms, it has begun to circumvent them, at least to some extent." Diggs is hopeful that FMVCC will succeed in opening the lines of communication among those in the malaria vaccine development community. One of FMVCC's goals is to develop mechanisms to increase private sector investment in malaria vaccine development.

Is the science there?

It could be argued (as it has been very vociferously by some) that a vaccine for malaria is an impossible pipe dream. The complex life cycle (*please see diagram accompanying article*) of the malaria parasite is perceived as one of the greatest challenges to designing a vaccine, as is the fact that correlates of immunity are not well known. That is, it is not clear which immune responses would be protective against the parasite and at which stage in its life cycle a certain immune response would be effective. Those working on malaria vaccine development have espoused several approaches; each tactic has consequences for the population who could most benefit from the vaccine. Transmission-blocking vaccines, targeting the sexual and sporogonic stages are under development, and would be of great benefit to individuals in geographically isolated areas and would prevent the reintroduction of the parasite in malaria-free zones. A pre-erythrocytic vaccine—that is, a vaccine that seeks to create immune responses to the parasite before it enters the blood cells, would be of greatest benefit, it is thought, to individuals traveling to malaria-endemic locales. For populations that live in regions where



Malaria is a parasitic protozoa of the genus *Plasmodium* and is transmitted through the bite of an Anopheles mosquito. The most common species of *Plasmodium* that cause disease in humans, *P. falciparum* and *P. malariae*, which is the most common and death. The female mosquito which bites a human in order for her eggs to develop, she bites a human, she injects her salivary glands with malaria parasites (1), which develop as sporozoites.

The sporozoites travel to the liver (4) where they develop within twelve days to mature into gametocytes. These gametocytes enter red blood cells and cause rupture (5), where they develop into asexual forms. The male and female gametocytes are produced and are in turn taken up by a mosquito when taking a blood meal. In the mosquito's stomach (3) develop into sporozoites and travel to the salivary glands. Sporozoites can be transmitted into another human when the mosquito takes another blood meal. In this stage, the development of the parasite is released from rupture of the red blood cells. The merozoites then travel to the liver. The clinical manifestations of malaria include fever, convulsions, and death. Breman and Murphy describe the disease burden in developing countries in their article. *Graphic of Clinical Biochemistry, Perth, Australia. Microscopical Diagnosis of Malaria Diseases* by Farbenfeld.

Successes and failures, points to great public health potential

malaria is endemic, and who are thus constantly exposed to and infected by the parasite, a blood-stage vaccine is viewed as essential for reducing disease burden. Both approaches are being explored in great detail by researchers in the Department of Defense (DOD), with considerable support for the blood-stage effort contributed by USAID.

The malaria vaccine program at WRAIR is developing pre-erythrocytic (RTS,S) and sexual stage (MSP-1) vaccines. In collaboration with researchers at the pharmaceutical company SmithKline Beecham, Rip Ballou and colleagues have produced the first malaria vaccine to reach Phase III clinical trials. Their sporozoite vaccine, according to Philip Russell, the founding president of the Sabin Vaccine Institute and a retired general in the U.S. Army who chaired an Institute of Medicine Committee on malaria vaccine development, proves that a vaccine is possible. "The WRAIR/SKB vaccine proves you can do it," he said. "You can get a protective effect and this gives us hope that we can move on to a blood stage vaccine that will be of great values to developing country populations."

At the NMRC Captain Stephen L. Hoffman has been working on a DNA vaccine in collaboration with Vical, a California biotechnology firm, with support from the DOD Military Infectious Diseases Research Program, the Office of Naval Research's Advanced Technology Development Program, the Federal Defense Laboratories Diversification Program and the pharmaceutical company Pasteur Merieux Connaught. In Phase I trials testing primarily for safety, tolerance and immunogenicity in humans, the vaccine was able to elicit cytotoxic T lymphocyte responses and was safe. This vaccine is directed towards the pre-erythrocyte stage parasites.

The most recent study to hit the scientific community, and even make it onto the network news, was conducted by researchers in the United States and in India. The experiments involved testing a multi-stage malaria vaccine that would, it was hoped, induce immunity to the various stages of the parasite. The rationale was that any vaccine based on only one stage of the parasitic life cycle would be necessarily

less efficacious than one that induced immunity in the host to the parasite and every stage of infection, from sporozoite, to liver-stage, to erythrocytic sexual to sexual stages. Researchers in the study immunized rabbits with a vaccine that contained synthetic genes encoding for antigens corresponding to the various stages. They found the vaccine to be highly immunogenic in the rabbit model. Future studies are needed to determine whether the vaccine is safe, immunogenic and efficacious in non-human primates and then in humans.

But the malaria research community has been burned before. In the early 1990s, Colombian scientist Manuel Patarroyo announced the results of studies that showed high efficacy of his SPf66 malaria vaccine. His results have yet to be duplicated elsewhere. But the optimism brought about by the initial announcement of the potential vaccine has taught malariologists to be cautious about contributing to false expectations. Ballou, Diggs and Hoffman have been humbled by the parasite as well. In 1987, they put their confidence in a vaccine directed to the circumsporozoite protein (CS) to the test: they were injected the vaccine in themselves and then were challenged by having malarious mosquitoes feed on them. Despite their confidence that the vaccine had worked, they both developed malaria infection.

Why the west should care

Despite the fact that malaria is perceived as a disease of the developing world, there are convincing arguments for the public and private sectors in developed countries to invest in research and development aimed at controlling or preventing the disease. Russell believes that the reason that the U.S. military is investing in malaria research is the threat it poses to America's troops. According to Russell, America's involvement in World War II "put the U.S. in an international mode,"

by pulling a generation of scientists and physicians out of academia and into the army. The NIH and USAID have also picked up the slack left by meager industry investment in the disease. Russell asserts that the current global effort is "totally insufficient. We need more money, and more effective interaction between biotechnology firms and the public sector."

The military threat, an angle espoused by Ralph Nader's Malaria Project, housed in the Center for the Study of Responsive Law (CSRL), is perhaps the most compelling and it is supported by the experience of the military in recent armed conflicts. According to Amir Attaran, the project's director, "A sick soldier not only fails to carry out a mission, but in a war situation, can delay troop movements and waste resources that are needed to fight an enemy." Furthermore, says Attaran, "History is full of wars lost because an Army was sick. In fact, in every war this century, soldiers have spent more time in the hospital sick with infectious diseases than with combat wounds." The CSRL's case is supported by the facts: in World War I, when influenza laid low or killed hundreds of thousands of troops; in Vietnam soldiers got over 600,000 cases of malaria; and in the 1990s in Somalia, malaria was the *number one* cause of hospitalization.

A second rationale for investment in malaria research is the increase in international travel that has been credited with the introduction of malaria in previously malaria-free regions. In recent years, the Centers for Disease Control (CDC) in Atlanta has reported 1000-1200 cases of malaria acquired abroad but diagnosed in the United States annually, though officials believe that an equal number of malaria cases go unreported. Thus, a traveler's market for a malaria vaccine would not be insignificant. According to NIAID director Tony Fauci, each year, approximately 30 million Americans are put at risk for contracting malaria when they travel to endemic countries.

In the 1996 IOM report issued by a committee chaired by Russell, *Vaccines Against Malaria: Hope in a Gathering Storm*, the blue-ribbon panel concluded that there needed to be more research on the market influences on investment in vaccine development. According to the report, "a clearly identified market is essential... traditionally most attractive markets have been thought to be the military and 'traveler' markets of North America and Europe—the vast emerging middle classes of South and Central America, Africa, India, and Southeast Asia, where the risk of malaria is widely recognized, have been largely ignored."

Russell contends that, until recently, there was little interest in understanding the principles of vaccine economics. Without this kind of information it is very difficult, if not impossible, to address the issues peculiar to vaccine research and development.

Lastly, should all humanitarian impetus fail, the socio-economic argument for controlling malaria is powerful. In its most simple form, it goes something like this: while malaria continues to stunt economic growth in developing nations, the United States and other developed countries are losing potential markets. Moreover, the political instability associated with countries ravaged by disease and little economic growth is a constant drain on Western foreign policy. This argument contends that it is the West's best economic interest to address the malaria problem. According to James D. Wolfensohn, president of the World Bank, malaria control is essential for economic development in Africa.

A reinvigorated effort to combat malaria

In the past two years, beginning most publicly with the International Conference on Malaria held in Dakar, Senegal in 1997, malaria has come into the spotlight. Much of this is due to the fact that the National Institutes of Health, the nation's premier source of funds for basic biomedical research, has put malaria and international health issues, on the research agenda. The origin of this emphasis is a good lesson in how the government, in particular the NIH, develops research priorities. At a meeting at the NIH convened in mid-summer 1995 between the Wellcome Trust, the Pasteur Institute and the NIH, the topic on the agenda was to identify areas in which the participants might develop productive collaborations and to plan the Dakar meeting. Scientists spent the entire day discussing many of the problems facing countries affected by diseases such as HIV and tuberculosis. The European delegation was concerned about the lack of scientific capacity and infrastructure within developing countries and suggested

that there needed to be more north-south, east-west collaboration to address some of these health issues.

At the end of the day, when it was time to settle on a disease focus for the Dakar meeting, the winning entry came from none other than Harold Varmus, director of the NIH, who had had research experience early in his career in India and was familiar with the problem of malaria. Thus began what can only be referred to as a reinvigorated effort to address malaria in a spirit of global cooperation with the NIH, through the National Institute of Allergy and Infectious Diseases (NIAID) taking an active role. At the Dakar meeting, the acronym, MIM, for the Multilateral Initiative on Malaria, was coined. The MIM is an alliance of organizations and individuals attempting to maximize the impact of scientific research against malaria in Africa. MIM's strategy is to work towards greater scientific capacity in Africa. According to John La Montagne, deputy director of NIAID, "At least two major themes were clear from the very beginning of the MIM and the NIAID effort to develop malaria vaccines and other interventions. The first of these is that there is a critical research need in the area and that this need had to be filled with collaborative efforts that actively engage African scientists as partners in this research and the African scientific establishment. The second essential element that was readily apparent was the need to work with control efforts in the region."

The NIH, says La Montagne, is involved in collaborative efforts with global agencies concerned with economic development and disease control, such as the World Bank. La Montagne asserts that the World Bank, "will indeed enhance its investment in Africa, not only in support of the health infrastructure that is needed for malaria control, but also in the general economic development of the region."

In addition to working with the World Bank, the NIH is coordinating its efforts with those of the WHO's regional office's in Africa and the African Development Bank, USAID, the Department for International Development (DFID) of the United Kingdom, and the European Union, among others. La Montagne believes that "these efforts will result in an increased level of economic activity in the region and ultimately and elevation of the standard of living for Africans. This will take time certainly and progress may be slow at first."

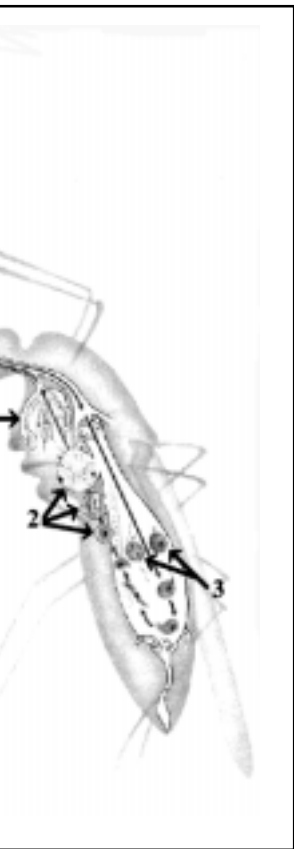
The very vocal and active role taken by the NIH may have been one of the factors leading to the Roll Back Malaria (RBM) campaign announced by Gro Harlem Brundtland last May, after becoming the new director-general of the WHO. Brundtland's vision for RBM is a global partnership, drawn from malaria affected countries, UN organizations, bilateral development agencies, development banks, non-governmental organizations and the private sector reduce burden of malaria. Though exactly how the WHO project will function is not totally clear, its emphasis on drugs for malaria might alarm those in the vaccine research community. The RBM program aims to cut malaria deaths by 75% by 2015. The feasibility of this goal, considering the emergence of resistant strains of malaria and limitations of vector control measures, is up for debate. As if overnight, malaria has become the hot disease, with a host of foundations and organizations springing up to advocate on its behalf.

Where to next?

If malaria is the "it" disease, does this mean that a vaccine is imminent? Maybe. The scientific challenges to developing a vaccine that is safe, efficacious, and accessible to the people who could most benefit from the vaccine, are formidable.

Conquering malaria will be one of the greatest feats of mankind. Not only would it be a scientific coup, but it would be an amazing humanitarian victory, providing a blue-print for how we can, as a global society, address health and development issues in a more productive fashion. With 40% of the world at risk for infection from a disease with enormous economic and social costs, controlling malaria is a humanitarian and economic imperative.

The challenges, however, can be overcome. The proof is in the science: scientists have demonstrated a level of success in developing a sporozoite vaccine, and thus we know that a vaccine is possible. There is great reason for optimism in the field of malaria vaccine development. Given a willingness to cooperate among researchers and policy makers, and the kind of financial support essential to such an endeavor, a malaria vaccine is possible.



a disease caused by the genus *Plasmodium* through the bite of the mosquito. There are four species that cause malaria disease: *P. vivax*, *P. ovale*, *P. falciparum*, the latter of which is the most common cause of infection. The parasite resides in the mosquito's midgut and requires a blood meal to mature (2). When the mosquito injects material from its salivary gland, which contains the mature parasite, this stage referred to

sporozoites move quickly to the midgut where they multiply, giving rise to thousands of merozoites. The young parasites develop in the liver cells when the liver cells they develop into sexual gametocytes. In the sexual cycle, gametocytes are produced and ingested by a female mosquito during another blood meal. In the stomach, the gametocytes develop into merozoites which migrate to the midgut and are then injected into a new host when the female mosquito takes another blood meal. In the asexual cycle, parasites are reared on red blood cells and invade new red cells.

Complications of the disease include anemia and Murphy describe the details in the accompanying article, *Chemistry, Royal Perth Hospital, Malaria; adapted from "The Malaria Parasite" by Dr. H. H. Henschen, published by Bayer, 1955.*

Scientist and Teacher: Herbert Herscowitz

BY ELIZABETH DE LA PAZ

"I wake up every morning happy to come to work," says Herbert Herscowitz, chair of the Scientific Advisory Committee of the Sabin Vaccine Institute and one of the Institute's greatest assets. His happiness stems from a 30-year professional career that includes positions in teaching, research, and various administrative appointments. Herscowitz is a professor of microbiology and immunology at the Georgetown University School of Medicine, two fields in which he became fascinated with early in his educational career; he believes that microbiology and immunology explain the essence of life. It was this attraction to the two fields that has led him to the professional success he enjoys today.

One testament to his personal achievements is his receipt of the 1998 Kaiser-Permanente Award for Sustained Teaching Excellence. According to Kenneth L. Dretchen, Dean of Research and Graduate Education, this prestigious award has only been given to a handful of select individuals who are chosen by a committee of students and colleagues. As Herscowitz began his professional career, he fell into teaching as an apprenticeship to a research position at the medical center. He was unsure of himself as a teacher at first, confessing that, "I was trained as an expert in a specific area of cellular immunology, and I found myself spending a great deal of time teaching medical and dental students. Yet when I began my career at Georgetown, I had never taken a course in education and therefore, I didn't know the right way to teach from the wrong way to teach."

Herscowitz has definitely overcome such feelings and has been recognized for his gift of teaching several times by his colleagues and students. He delights in working on a one-to-one basis with the medical students, watching them "acquire information and develop into individu-



Herbert Herscowitz presents a book award for creativity and initiative in scientific research to Eileen Tschetter at the annual Junior Science and Humanities Symposium in January 1999.

als who have the necessary skills that can be applied for the benefit of society."

His current research activities focus on immunological approaches to the treatment and prevention of cancer. He collaborates with several Lombardi Center laboratories that are involved in developing immunologic approaches to controlling cancer, specifically tumors of the breast, brain, and prostate gland. According to Herscowitz, the best part of his current research effort is the feeling that he has "the potential to save someone's life directly."

One of the most recent contributions Herscowitz has made to the Sabin Vaccine Institute is the development of the Sabin-Hilleman Fellows Program, which gives local high school students opportunities to take part in research activities aimed at preventing disease through the development and administration of vaccines. He sees the program's goal as an

opportunity to get young people excited about academic scientific research at an early age, so that they may "become not only a scientist, but also a transmitter of information to others." It is a chance to inspire and direct the young students into rewarding careers in vaccinology and immunology, in which they can develop new ideas as well as follow in other's footsteps.

Despite the numerous daily responsibilities, Herscowitz believes that the challenge of trying to balance everything in his life gives him the stimulus to continue. "If I had nothing to do, I'd be very unhappy," he says. He is satisfied with his current status in life, both personally and professionally and is most proud of the great successes of his wife, their children, and the families they have started in turn. A century from now, Herscowitz hopes to be remembered for the impact he has made on young people by helping them reach their full potential. ❖

Aerosol Measles vaccine workshop draws on researchers from Mexico, CDC, FDA

BY CHARLENE A. FLASH

For many people, old and young, the thought of a needle injection is an unpleasant one. Needle injections are also more cumbersome and require more rigorous storage and transportation conditions than orally delivered medications. These issues and others inspired Albert Sabin, who developed the oral polio vaccine and for whom the Sabin Vaccine Institute was named, to devise methods of vaccine delivery which were non-threatening and cost-effective. Sabin performed research on an aerosol delivery system for the measles vaccine, in the laboratory of Joseph A. Bellanti, now senior vice-president of the Institute.

Continuing the legacy of Sabin, the Institute hosted the Aerosol Measles Immunization and Alternative Routes of Immunization Workshop on January 13, 1999. Public health officials and scientists from in-



Hopkins' Diane Griffin and Stanford's Yvonne Maldonado attended the workshop.

dustry and academia in Mexico and the United States gathered to discuss the global impact of measles. According to Bellanti, the workshop was "meant to bring together those active in the field to review where we have been, where we are, and where we are going."

The complications associated with needle injection of vaccines are not new. In a 1998 talk given at a National Foundation for Infectious Diseases press conference, the Center for Disease Control's (CDC) Bruce Weniger, assistant chief of vaccine development National Immunization Program at CDC, remarked about the impact of having so many vaccination requirements delivered by needle injection. "Many providers and parents," he said, "are reluctant to administer so many injections during a single visit because of the child's fear of needles and pain. This results in deferred vaccination, additional time and cost for follow-up visits and potential disease if follow-up is delayed or missed." Furthermore, con-

tinued Weniger, "Needles and syringes have additional drawbacks such as unsterile reuse in developing countries, improper disposal and needles-stick injuries."

At the measles workshop, the CDC's Peter Strebel reported on the state of measles in the world and described the need for trained health workers, a "cold chain" for vaccine transport, needles, syringes, and auto-destruct carrying cases. He also discussed the danger measles posed in areas where there are very few cases, comparing the disease to "a sleeping giant." He elaborated: "Sometimes when the public sees zero cases they get lax in getting vaccinated."

Jorge Fernandez de Castro, a past associate of Sabin, shared the testimonials of Mexican parents who greatly preferred aerosol vaccines over injected vaccines, and described the incredible effectiveness of the aerosol technique in eradicating measles in Mexico. There are currently on-going clinical trials in Mexico. Yvonne Maldonado, of the Stanford University School of Medicine Department of Pediatrics, gave an epidemiological overview of vaccine efficacy. Maldonado stressed the need for geographically specific programs.

The workshop ended with a brainstorming session, facilitated by Mark Papania, the acting Chief of the Measles Elimination Activity National Immunization Program at the CDC, and James J. Barry, Principal Engineer at CREARE, Inc, who succinctly described the logistical specifications of an aerosol device suitable for the measles vaccine.

Members of Bellanti's research group continue to work in tandem with Mexican scientists and officials to perfect the aerosol measles and rubella vaccine.

Countdown to polio eradication continues

BY JESSICA QUINN

A world free of the ravages of Poliomyelitis may be a reality with the arrival of the new millennium. The World Health Organization (WHO) reports that elimination of the disease would save the world an estimated \$1.5 billion on immunization expenses alone, not counting the cost of treating Polio victims. However, \$800 million is needed to ensure the complete riddance of Polio.

In May of 1988, the World Health Assembly predicted the eradication of Polio by the year 2000. This marked the beginning of an extensive four-step plan to eliminate the virus that attacks the central nervous system. Poliomyelitis usually enters through the mouth and spreads along the nerve cells often resulting in permanent paralysis as well as fatigue, fever, vomiting and constipation.

Control of the disease began in 1954 when a vaccine designed by Jonas Salk was declared safe and mass inoculation began.

In 1963, Albert Sabin developed an oral vaccine called Trivalent Oral Polio Vaccine (OPV)

In India, 130 million children were immunized in a single day.

which replaced Salk's injectable vaccine (IPV). The existence of this effective and inexpensive vaccine has been the key to eradication.

The first step in the process is routine immunization. Second, mass immunization campaigns are highlighted by National Immunization Days (NID). During NIDs, every child under five years of age is inoculated with 2 doses of OPV. A recent NID in India immunized 130 million children in a single day. The third step, surveillance, calls for the rapid reporting of suspected cases. Lastly, Mop-Ups, or house to house immunizations are conducted in high risk areas.

Since the implementation of these steps in 1988 the number of Polio cases has declined nearly 85%. Polio has already been eradicated from North and South America and most of Europe. Meanwhile, it is still endemic in South Asia and Sub-Saharan Africa.

The world will be certified as free of polio three years after the last confirmed case. Until then, immunizations will continue until eradication is achieved, now predicted to occur around 2010. ❖

Matters of giving

BY DIANE MYERS, DIRECTOR OF DEVELOPMENT

Many of the initiatives that you have read about in this issue of the *Sabin Vaccine Report* were made possible through the generosity of many donors. Philanthropic support is critical to the success of our efforts in supporting vaccine research, advocating for sound public policy, and educating the public about the enormous benefits of immunization.

One of the Sabin Vaccine Institute's newest initiatives is its Sabin-Hilleman Fellows Program whose goal is to increase the number of bright young scientists who choose careers in vaccinology. This summer we will bring ten high school students to the Georgetown campus and give them hands-on research experience in the biological sciences. We will also provide learning opportunities in public and health care policy issues surrounding vaccines. ❖

Gates donates \$100 million to children's vaccines

continued from page 1

in the science of vaccine development as well as the public policy aspects, the CVP is poised to have major impact on world health. "It directly addresses the difficult and complex problem of delivering the new vaccines to children in the developing world," he said. He continued, "The program brings resources, innovation, and an entrepreneurial approach to the field which will complement the efforts of the U.N. agencies."

Hepatitis B vaccine leads to major decline in disease

BY JESSICA QUINN

As much as 20% of the population in the areas of China, Southeast Asia and much of Africa is infected with Hepatitis B virus, despite the existence of an effective vaccine. In the United States less than five percent of the population is infected. The majority of cases in the U.S. involve adults while in Asia and Africa mostly children are afflicted, contracting the disease from their mothers during birth.

A vaccine against Hepatitis B has been available in the United States since 1982. The original was plasma derived while the Hepatitis B Vaccine presently used is obtained from recombinant yeast cells. In the new, safer vaccine, yeast cells are genetically altered to produce the Hepatitis B surface antigen. The body recognizes an antigen as a foreign molecule and begins to produce antibodies to eliminate it. Vaccines work by fooling the body into making the antibodies against a particular antigen, thus creating a state of protection against the disease. The recombinant vaccine is administered in three doses. After the third dose, the vaccine is reported to be 85-95% effective. Since 1985, Hepatitis B infection in the United States has fallen by 55%.

This decline in Hepatitis B infection is attributed to both the existence of the vaccine and awareness among high risk groups. Children under 20, health care workers, injection drug users, sexually active heterosexuals and homosexual men are all strongly advised to get vaccinated. For more information on Hepatitis B, please visit the Sabin Vaccine Institute Website or call the CDC at 1-888-4-HEPDO. ❖

The Children's Vaccine Program will support various activities in an effort to improve access to vaccines and immunization rates. Research related to the "field effectiveness" of the four vaccines, the economic and social costs of diseases, and analyses of the cost-effectiveness of preventing those diseases will be a major aim of the CVP. This information will be invaluable to health program managers as they make plans for future use of the vaccines. In addition, the CVP will support model immunization programs in selected countries to establish the most cost-effective means of introducing the new vaccines and will fund international meetings and conferences aimed at developing consensus on use of the vaccines.

Russell is pleased with the approach taken by the Gates' and PATH. "The economic barriers to vaccinating children in the developing world are formidable and new approaches and innovative solutions are needed. The CVP, working with governments in the poorest areas of the world,

will have a very important impact on the health of children."

The Gates program will focus on increased communication as well by supporting the creation of an international information program to generate support for rapid introduction of the new vaccines and to help build global markets so that prices can be lowered. Additional goals include designing activities to ensure an adequate and competitive supply of vaccines and to develop funding mechanisms to supply vaccines to countries in need and spurring efforts to create new and diversified financing mechanisms to support childhood global immunization.

PATH was founded in 1977 to improve health, especially for women and children. The organization emphasizes improving the quality of reproductive health and preventing and reducing the impact of widespread communicable diseases. ❖

Americans for Medical Progress honor Albert B. Sabin "Heroes of Science"

On January 14th, the Americans for Medical Progress honored Barbara Barry, Thomas B. Clarkson, Laurie Flynn, United States Senator Connie Mack and his wife Priscilla, Patricia S. Schroeder, Beverly Sills and Dennis J. Slamon.

Heloise Sabin, widow of the late Albert Sabin, and a founder of the Sabin Vaccine Institute, attended the event. "I was privileged to help present the AMP's Sabin award," she said. "The award is a wonderful tribute to Albert's dedication to scientific excellence and progress." ❖



Beverly Sills, Barbara Barrie, Heloise Sabin and Patricia Mack (l to r) participate in the 1999 Albert B. Sabin Heroes of Science Awards ceremony.

photo courtesy of TISARA

Rotavirus, from page 1.

Now that the vaccine has been developed and has won FDA approval the question remains as to whether or not the children who need it most, those living in developing countries, will ever receive it.

The biology of rotavirus and Rotashield™

Rotaviruses are part of the family *Reoviridae*, which are characterized by their double-stranded, segmented, RNA genomes. Each segment codes for a specific viral protein, however, these codes can vary within a population of viruses, resulting in different viral strains. Because of their genomes, rotaviruses can undergo reassortment, which is the exchange of gene segments during the coinfection of more than one strain. Reassortment enables rotaviruses to generate diversity, an evolutionary tactic which enhances their ability to evade the host's immune system. The distribution of serotypes varies geographically, with particular strains found primarily in developed nations and others in developing nations.

RotaShield™ is a live vaccine developed against most common serotypes. The vaccine is orally administered in three doses, recommended at ages two, four, and six months. In efficacy trials in the United States, this vaccine was found to protect against approximately 50% of all rotaviral related disease, and 64-100% of severe disease. In developing nations, however, the results of efficacy trials were not as decisive and were less consistent. Trials in Venezuela, Peru, and Brazil demonstrated a range of 24-48% protection from all rotaviral disease and 0-88% protection against severe disease. These numbers could reflect complications due to the interference of other enteric diseases or problems following up on patients' progress. The trial in Venezuela was the most successful and gives hope for the possible benefits of a large-scale vaccine initiative in developing nations.

In the United States rotaviral infections follow a temporal and geographical pattern, with the prime rotavirus season beginning in the Southwest in autumn and moving in to the Northeast by spring. Globally, other areas with temperate climates also have a peak rotavirus season in the fall and winter, however, in tropical environments and typically in developing nations, there is a much

more diffuse epidemiology. The virus is typically spread by the fecal-oral route, although there is some debate as to whether the virus can be transmitted through respiratory secretions.

Clinical manifestations of rotaviral disease

In most cases, children first infected with rotaviruses initially experience a temporary bout of diarrhea and possibly fever and vomiting then recover with a partial immune resistance to further infection. In some cases though, the infection is more severe and children can become fatally dehydrated. Oral rehydration therapy, or if necessary, hospitalization and intravenous fluids, are the most common treatment methods in developed countries. These therapies are not readily available in most developing nations, however, where poorer health in general increases the chances of developing severe and possibly fatal disease. This situation is glaringly apparent when comparing the effects of rotaviral infections in developed nations, particularly the United States, with those in developing nations. *In the United States, approximately one in 30,000 rotavirus infections is fatal, however, that ratio rises to one in 150 in developing nations.*

More vaccines on the way?

Although RotaShield™ is the only rotavirus vaccine currently licensed by the Food and Drug Administration, others are being developed. Some of these use a non-Jennerian (live virus) approach in an effort to increase the protection conferred by the vaccine against both mild disease as well as moderate to severe forms of infection. Both Merck and SmithKline Beecham are currently field testing rotavirus vaccines and investigating the relationship of strain variety in the vaccine to the resulting protection, but these are probably two to three years away from approval. In addition, scientists at the Cancer Research Institute (CRI) of Contra Costa in California found that lactadherin, a glycoprotein found in breast milk, inhibits rotavirus activity in vitro. CRI is working on the development of a genetically engineered lactadherin that would protect against the development of the symptoms of rotavirus infections by selectively binding the putative receptor associated with the development of diarrhea. Such a product could be used to

supplement infant formula or even for administration to susceptible adult populations, such as those with weakened immune systems.

The success of RotaShield™ is encouraging, but there is still a long way to go before all children can benefit from its success. RotaShield™ is administered orally and does not require special storage conditions such as refrigeration, both of which make distribution of the vaccine in developing countries more feasible. However, at approximately \$38 per dose, RotaShield™ is unaffordable in these countries. It has been proposed that if the pharmaceutical companies manufacturing a vaccine (which right now only includes Wyeth-Ayerst) are able to charge a higher price in developed nations, they will be able to offer it to developing nations at a greatly reduced price. However, before the vaccine can be distributed in these countries, more research is needed.

For example, there is little data describing the effect of administering the vaccine to children who are infected with HIV who might be susceptible to infections caused by the vaccine itself. The report on RotaShield™ by the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention states that RRV-TV should not be given to infants with known or suspected immunodeficiency though they recommend it for healthy children. The situation is complicated by the fact that in developing nations, many adults, and therefore children, are not even aware of their HIV status. Regarding these issues Glass admits that it is "hard to make a recommendation one way or the other so the first recommendation is one of caution until we know more." These questions will hopefully be addressed by ongoing studies to facilitate the distribution of an effective rotavirus vaccine to those in most desperate need.

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Rachel Liberatore is a research assistant in the Laboratory of Molecular Genetics and Immunology of Jeffrey V. Ravetch at The Rockefeller University in New York City. She graduated in 1998 from Princeton University with a degree in molecular biology.

News from the Sabin Vaccine Institute

Patricia Thomas awarded Leonard Silk Journalism Fellowship

Patricia Thomas, a frequent contributor to *Sabin Vaccine Report* and a Research Fellow of the Sabin Vaccine Institute, has been awarded the Leonard Silk Journalism Fellowship. This \$30,000 prize will enable Thomas to move ahead with her book on AIDS vaccine research, an endeavor that has also been backed by the Albert B. Sabin Vaccine Institute. Thomas' book will be published by *PublicAffairs*.

"Immediately after I learned about the award, I was invited to an important AIDS vaccine meeting in Africa and offered an inside look at two pioneering vaccine trials in Thailand," Thomas said. "Thanks to the fellowship, I'm going to be able to do both. It came just in time."

The Silk Fellowship was endowed by the family and friends of the late *New York Times* economics columnist Leonard Silk, and is meant to help an established journalist complete a book on an important contemporary issue. It is administered by The Century Foundation/Century Fund in New York, and is awarded to only one author each year. ❖

Immunization conference held

Immunization program leaders gathered at the "Every Child By Two (ECBT) Immunization Partners Conference in Washington, DC on December 7-8, 1998 to share successful strategies for raising vaccination rates.

ECBT was founded by former first lady Rosalynn Carter and Betty Bumpers, former first lady of Arkansas, to ensure that all of America's children are fully immunized on schedule, from birth to two years of age. Conference presentations covered the latest strat-



Institute senior vice president Joseph Bellanti meets with former first lady Rosalynn Carter.

egies to raise immunization rates above 90%, and to maximize the effectiveness of state children's health insurance programs, vaccine partner outreach activities and school-based immunization activities.

The Sabin Vaccine Institute was represented by its Senior Vice President, Joseph A. Bellanti. ❖

Institute sponsors translational research colloquium

Scientists gathered at the Banbury Conference Center at Cold Spring Harbor in mid-December to discuss issues in translational research. The colloquium, *Translational Research: From the Bench to the Bedside*, was part of an on-going effort at the Institute to encourage interaction between individuals involved in all aspects of pharmaceutical development. Basic scientists and industry representatives discussed the challenges faced by researchers in



Vaccine research Mike Levine, Cold Spring Harbor president Jim Watson, colloquium chair Peter Hotez and Institute Chairman H.R. Shepherd.

bringing a product from idea to design to testing to market. The colloquium was chaired by Peter Hotez, chair of the International Council of Scientific Advisors at the Institute, who is a professor of pediatric infectious diseases at Yale School of Medicine.

Hotez, who is actively involved in developing a vaccine for worm infection, sees the colloquium as the starting point for more collaboration among vaccine researchers and hopes that, this and future colloquia "lead to the creation of a translational vaccine network that will help facilitate the development of the next generation of vaccines, both here and abroad."

Sabin Honors Student at Junior Science & Humanities Symposium

On January 8th, the Institute presented Eileen Tschetter, a 10th grader at Washington-Lee High School in Arlington, Virginia, with an award for Creativity and Initiative in Scientific Research for her research on the flammability of sleepwear. Her paper, entitled "Sleepwear: A Burning Issue," was entered in the annual Junior Science and Humanities Symposium (JSHS) at Georgetown University School of Medicine. Ms. Tschetter's goal was to test if there was a difference in the ignition time of fire retardant and untreated 100 % polyester fabric.

JSHS was founded in 1958 and is currently funded by the US Army Research Office, the Air Force Office of Scientific Research and Office of Naval Research. ❖



photo by Erica Seiguer

Institute debunks anti-vaccine propaganda

The Sabin Vaccine Institute refuted a story spread by anti-vaccination activists that alleged that certain forms of cancer may have been caused by injected polio vaccine manufactured before 1961. Interviews with Institute senior vice president Joseph A. Bellanti were included in news broadcasts by CBS Radio News and NBC4 television in Washington. The stories accurately reported the absence of scientific evidence of the alleged vaccine-cancer link. Bellanti and other experts said other risk factors, such as smoking and exposure to asbestos, are associated with the cancers. They stressed the stringent safety testing that vaccines undergo and urged the public to continue getting vaccinated against polio.

IDSA announces availability of Immunization News Briefs

With grant support from the Robert Wood Johnson Foundation, the Vaccine Initiative, a special project of the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society, announces the availability of a free news service, *Immunization News Briefs*. This news resource brings immunization news to your computer three days a week. This service will focus on immunization efforts, vaccine development, and disease outbreaks throughout the world as reported in the 1,400 news sources that are regularly reviewed, including major newspapers and magazines; regional, national, international, and business wire services; weekly and monthly trade journals; business periodicals; legislative sources and non-industry sources.

Delivered via e-mail on Monday, Wednesday and Friday, the condensed abstracts of the news about immunization and vaccine issues, *Immunization News Briefs* provides a comprehensive, yet concise, report on the latest news, issues and developments about and affecting the immunization program. *Immunization News Briefs* will also keep you up to date on pending federal and state regulation, new product developments, and trends in vaccine development as reported in the press and scientific literature. In addition, this news will remain in a searchable archive on the Vaccine Initiative's home page (within the IDSA's web site).

Subscribe to *Immunization News Briefs* at <http://www.idsociety.org/regform>

Sabin Gold Medal to be awarded to founding president of Institute

Philip K. Russell, the founding president of the Institute, will be awarded the Albert B. Sabin Gold Medal Award at the Second Annual Conference on Vaccine Research in Bethesda, Maryland on March 28th, 1999. The Gold Medal was created in 1994 to recognize individuals who have made major contributions to vaccinology and, in so doing, have improved the human condition. Previous recipients include D.A. Henderson, Robert M. Chanock, Joseph L. Melnick, Maurice R. Hilleman, Myron M. Levine and Allen C. Steere.



Russell received his A.B. degree in biology from Johns Hopkins University in 1954 and his M.D. from the University of Rochester in 1958. After an internship in medicine at North Carolina Memorial Hospital, he entered the United States Army Medical Corps in 1959. He completed residency training in internal medicine at University Hospital in Baltimore and was board certified in 1965.

During his military career, Russell conducted research on a variety of infectious diseases of importance to the military and managed several vaccine development programs.

Military assignments included several positions at Walter Reed Army Institute of Research, including Chief of the Department of Virus Diseases, Director of the Division of Communicable Diseases, Deputy Director and Institute Director and Commandant. Russell served as Commander of the U.S. Army Medical Research and Development Command (1986-90), and retired as a Major General in 1990.

Russell's military awards include the Legion of Merit and the Distinguished Service Medal. He received the Gorgas medal for contributions to preventive medicine and the Joseph Smadel medal and lectureship. Following military service he was appointed Professor in the Department of International Health at the Johns Hopkins University School of Hygiene and Public Health.

Russell has served on many national and international advisory groups including the Institute of Medicine Committee on Microbial Threats to Health, and the President's Advisory Committee on Human Radiation Experiments. He was a member of the Board of Scientific Counselors of the National Center for Infectious Diseases. Dr. Russell served as Special Advisor to the International Children's Vaccine Initiative and is on the Board of Directors of the International AIDS

sabin calendar

The Institute is not responsible for non-Institute events listed below.

March 17-20, 1999

Walker's Cay, The Bahamas

COLLOQUIUM ON CANCER VACCINES AND CANCER IMMUNOTHERAPY

Co-chaired by Drew Pardoll, the Johns Hopkins University School of Medicine and James P. Allison, the Cancer Research Laboratory at the University of California-Berkeley.

March 28-30, 1999

Bethesda, MD

SECOND ANNUAL CONFERENCE ON VACCINE RESEARCH
Sponsored by the National Foundation for Infectious Diseases, the Centers for Disease Control, the International Society for Vaccines, the Center for Biologics and Evaluation at the Food and Drug Administration, the Children's Vaccine Initiative, the World Health Organization and the Albert B. Sabin Vaccine Institute at Georgetown University.
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