By Jane BocVeld

Against the Grain

Unlike most, Dr. Harvey Pass believes in early detection screening for those at high risk for lung cancer.

FOR A FELLOW WITH CANCER, BART LAZARUS IS A LUCKY MAN. In 2006, he was diagnosed with lung cancer, but when NYU surgeon Dr. Harvey Pass removed the tumor, it was only, in Lazarus's words, "about the size of a grain of rice." He was back on his feet in a couple of weeks. He didn't need chemotherapy or radiation and so far remains cancer-free. "The hardest part of the whole thing was giving up smoking," says the 65-year-old Lazarus, who smoked about three packs a day for 50 years. "I had my last cigarette walking into the hospital for surgery."

How was Lazarus's cancer caught so early when the vast majority of lung cancers aren't diagnosed until Stage 3 or 4, by which time they are almost always fatal? The answer: he was being screened. In 2002, Lazarus's internist decided to send him for a computerized tomogram (CT) of the chest when he expressed concern about some breathing problems. This was an unorthodox step. No major medical organization recommends CT scanning for early detection of lung cancer, even for patients at high risk. Thanks to annual screening, Lazarus's cancer was caught in time.

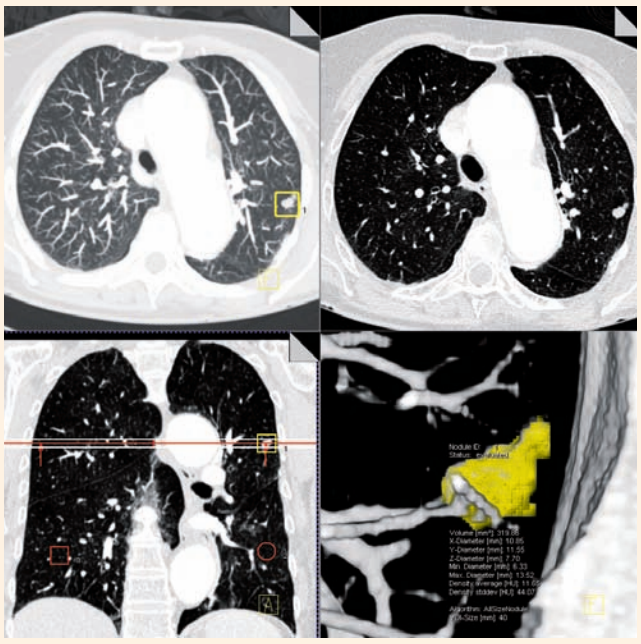
More than 160,390 Americans died of lung cancer in 2007, according to the National Institutes of Health. That's more than one-quarter of all cancer deaths. According to the American Lung Association, about 87 percent of those cases are caused by smoking. Another 12 percent may be linked to radon, a naturally occurring radioactive gas that seeps into homes and can rise to dangerous levels. Exposure to carcinogens, such as asbestos, on the job is also responsible. Because late diagnosis contributes to the deadliness of the disease, many researchers, including Dr. Pass, are conducting studies to establish a protocol for early screening. At present, a number of potential screens are being investigated, including breath and blood tests, CT scanning, and fluorescence bronchoscopy.

Dr. Pass, professor of cardiothoracic surgery who heads the Division of Thoracic Surgery and Thoracic Oncology, has advocated early screening for more than a decade. After serving as the chief of thoracic oncology at the National Cancer Institute (NCI) from 1986 to 1996, where he conducted surgical trials in locally advanced lung cancer, he says, "I saw where the field has to go, and that's early detection."

He's been assessing early-detection scans ever since and believes there is enough evidence to expand the use of CT scans at medical centers that follow certain protocols. One of the difficulties with this method of screening, however, is the high number of false positives. CTs may also show nodules and lesions that are benign, leading to unnecessary biopsies. That's one of the reasons that none of the major medical organizations recommends CT scanning to screen for lung cancer. CT scans detect very small nodules, much smaller ones than X-rays can show. Some of these nodules are benign and some are not, but all will be monitored with a scanning protocol. That's expensive for the health-care system and may put patients through unnecessary surgery.

Nevertheless, a number of researchers, including Dr. Pass, contend that, as he puts it, "there is a survival advantage" to CT scanning. For evidence, he points to a large, multicenter study conducted by the International Early Lung Cancer Action Program. That study screened more than 30,000 high-risk people using low-dose CT scanning from 1993 to 2005. During that period, 484 cancerous tumors were found; 412 were Stage 1, early enough to be treated successfully. Along with other researchers, Dr. Pass is waiting for the findings from an even larger NCI study, due out in 2009, to see if they confirm this study.

Because of its high false-positive rate and high cost — a CT scan runs about $300 and would need to be done annually — researchers are also looking for other ways to do initial screening. One alternative is already being tested. In a study published last year, led by Michael Phillips, M.D., who heads Menssana Research, Inc.,



Top Panel:
Transverse CT images of the chest. The image on the left reveals a nodule (yellow box) in the left upper lobe of the lung.

Bottom Panel:
A different view of the same patient's lung using CT. A reconstructed 3-D image, right, shows the volume of the nodule. The growth of the nodule can be assessed by following changes in the volume measurements of the nodule.

IMAGES COURTESY OF DR. HARVEY PASS

it was reported that a two-minute breath test may successfully screen for lung cancer in high-risk patients. The test measures chemicals called volatile organic compounds (VOCs), primarily alkanes, that change when someone has lung cancer, diabetes, breast cancer, or other diseases. Interestingly, VOCs vary with each disease, so the composition of chemicals in the breath of a patient with lung cancer will be different from that of a patient with breast cancer. According to the 2007 article in the journal *Cancer Biomarkers*, the patterns are "sufficiently distinctive to constitute a virtual 'fingerprint' of a disease." Dr. Pass, one of the study's authors, is currently enlisting patients for a follow-up clinical trial.

Another biomarker that holds promise for early detection is osteopontin, a protein found in the blood. Certain cancers, including lung cancer, cause the body to produce more osteopontin. Dr. Pass conducted a study that examined osteopontin levels in the blood of workers who had jobs that put them at high risk of being exposed to asbestos (miners, factory workers, carpenters, electricians, and railroad workers) and compared these levels to patients with the asbestos-induced cancer called mesothelioma. The levels were markedly different between the two groups. A larger study to validate the findings is warranted, he says.

Lung cancer also develops in the bronchial tubes. But CT scans don't show the airways well, so a bronchoscopy is used to examine them. In this procedure, the physician guides a small, flexible lighted tube down the throat into the bronchial tubes to look for nodules or other abnormalities. Traditional bronchoscopy has difficulty distinguishing cancerous from noncancerous lesions, but a new procedure, called fluorescence bronchoscopy, approved by the FDA in 2005, can highlight cancers. "We shine a blue light into the airway," Dr. Pass explains, "so you can see the areas that are abnormally fluorescent — they look black, red, or salmon colored. These are the areas that need to be biopsied."

Given the rapid pace of research, Dr. Pass predicts that there will be effective screening tests for early-stage lung cancer within the next five years. Until then, he encourages his patients who are at high risk to find doctors and hospitals, such as NYU, that are part of the Early Lung Cancer Action Program. "That's the ideal place to enter into a screening program." ●

IMAGE: GETTY IMAGES

Solving a Riddle About Malaria Protection

A SCHOOL OF MEDICINE SCIENTIST appears to have found an answer to a longstanding riddle about why alpha thalassemia, an inherited blood disorder, protects against malaria. "It is really remarkable and so simple," says Karen Day, Ph.D., professor and chairwoman of medical parasitology, who led a research team that recently published their findings in *PLoS Medicine*.

"We made the surprising finding that packaging your hemoglobin in smaller amounts in more cells is an advantage against malaria," says Dr. Day. Hemoglobin is the oxygen-carrying protein in red blood cells.

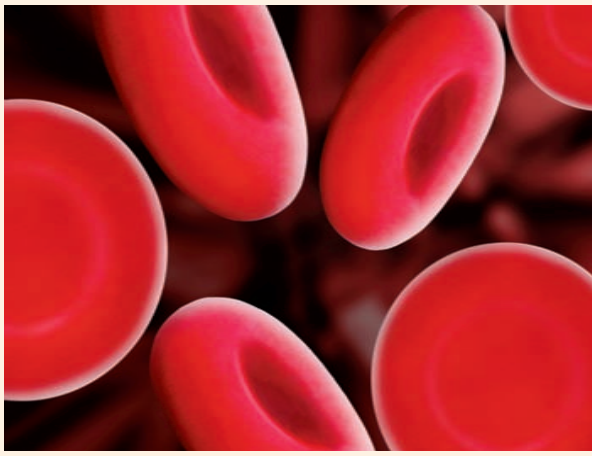
"Children with alpha thalassemia adapt to the loss of red blood cells associated with malarial disease by making more of these cells with less hemoglobin," says Dr. Day. "So, when they have a malaria attack they do better because they end up with more hemoglobin overall compared to normal children," she says.

Malaria, a mosquito-borne disease, afflicts hundreds of millions of people, causing up to 2 million deaths every year in Africa and Asia. Many of its victims are young children. Although parasitologists have known for decades that the blood disorder alpha thalassemia protects against malaria, they weren't sure why. Many speculated that the disorder produced red blood cells that were impervious to the parasite that causes malaria, which spends part of its life inside these cells and eventually destroys them.

In fact, Dr. Day's team did find the malarial parasite in the blood of children with thalassemia. But another finding helped solve the mystery of why these children were not dying from malaria.

Alpha thalassemia is common in Asia, the Mediterranean, and Melanesia, where malaria is or was prevalent. In the mid-1990s, researchers working on the north coast of Papua New Guinea proved that children with mild alpha thalassemia who inherit mutations in the "alpha" hemoglobin genes from each parent were protected against malaria. These children were 60 percent less likely to get severe malarial anemia than normal children.

Dr. Day and colleagues based their new study on this same population of children. They found that one-third to one-half of the total number of red blood cells were lost following an attack of severe malaria. But the children in the study with mild alpha thalassemia tolerated this massive loss because they started out with 10 to 20 percent more red blood cells than unaffected children.



Red blood cells

According to the National Human Genome Research Institute, most people with alpha thalassemia have milder forms of the disease, with varying degrees of anemia. The most severe form mainly affects individuals of Southeast Asian, Chinese, and Filipino ancestry and causes fetal or newborn death.

Authors of the study are Karen P. Day; Freya J.I. Fowkes, who was a Ph.D. student in Dr. Day's laboratory and is now at the Walter and Eliza Institute of Medical Research in Melbourne, Australia; Angela Allen and David J. Weatherall, University of Oxford; Steve Allen, University of Swansea, and Michael Alpers, Papua New Guinea Institute of Medical Research. ●

By Josie Glausiusz

To Feel Pain and Cry Again

MICHAEL BRENNER WAS BORN WITH a mystifying constellation of symptoms: feeding problems, persistent vomiting, delayed development. For two years, his parents trailed along with him from doctor to doctor until a neurologist finally told them that he suspected that their boy had familial dysautonomia (FD), a rare genetic disease that occurs in one in 3,000 live births in the Ashkenazi Jewish population. The prognosis was grim: Michael was unlikely to live beyond the age of five.

Today Michael is 20 years old, and while he has learning disabilities, his health is stable, and he has beaten the odds. His father, David Brenner, is the executive director of the Dysautonomia Foundation. He was appointed to his present position in 2006 after 16 years of volunteering for the organization. His dedication, he says, was inspired in part by the care and compassion of Michael's physician, Felicia B. Axelrod, M.D., the Carl Seaman Family Professor of Dysautonomia Treatment and Research and professor of pediatrics and neurology. As the world's foremost expert on the disorder, she has devoted 37 years to investigating the causes and the treatment of FD. That persistence has finally paid off: she and her colleagues at NYU's Dysautonomia Treatment and Evaluation Center may have discovered a compound, kinetin, that could potentially correct the FD gene mutation.

It was Dr. Axelrod who definitively diagnosed Michael when he was two years old and immediately suggested surgery to prevent food regurgitation, and the insertion of a feeding tube into his stomach to ensure adequate nutrition. These measures have enabled Michael and many others with FD to reach adulthood. In fact, 50 percent of those diagnosed with the disorder now reach the age of 40.

It was not always so. FD affects the autonomic nervous system, the "orchestra leader" that keeps the rest of the nervous system in balance. A mutation on chromosome 9 — identified in 2001 in collaboration with Harvard geneticists — inhibits the ability of a gene called IKBKAP to make a protein called IKAP, which controls the development of neurons. One in 27 Ashkenazi Jews carries one copy of the mutation, which is recessive; in other words, an affected child must have two copies, one inherited from each parent. Symptoms of FD include partial or complete inability to feel pain, heat, or cold; lack of overflow tears (leading to abrasion of the cornea); and repeated bouts of pneumonia due to aspiration of food particles into the lungs. Although surgery and drugs can ameliorate some of these symptoms, the disease progresses relentlessly as patients age.

It was with this adult population in mind that Dr. Axelrod sought a drug to modify the mutant gene in order to treat symptoms. These days, fewer than five children with FD are born each year (down from 15 to 20 per year) thanks to carrier and fetal screening. "But what do you do for the patient who already has it?" asks Dr. Axelrod. That's why she collaborated with human geneticist Susan Slaugenhaupt, Ph.D., of Massachusetts General Hospital to screen therapeutic drugs, examining about 100 until they found a plant hormone called kinetin that corrects the FD gene's activity in cell culture. Kinetin enhances the production of normal IKAP, which itself is part of a protein complex called Elongator that regulates the expression of about 100 other genes, some of which are involved in cell migration and development. A subsequent study at NYU on the effect of kinetin on carrier parents (who have only one copy of the gene) shows similarly promising results. Thus kinetin, and possibly other drugs, can modify the FD gene's expression and offer patients like Michael new therapies.

But genetic intervention is just one of the center's goals. Last fall, a $2.5 million grant from the Dysautonomia Foundation enabled Dr. Axelrod to recruit Horacio Kaufmann, M.D., the Felicia B. Axelrod Professor of Dysautonomia Research and professor of medicine, pediatrics, and neurology. An eminent researcher who specializes in autonomic disorders, he will treat adults with FD. In addition to being named co-director of the center, Dr. Kaufmann is also director of a new Dysautonomia Research Laboratory. The grant will also fund the expansion of the center, doubling its current space.

Dr. Axelrod has started testing kinetin, as well as some other promising drugs, on FD patients and hopes, in the long term, to stop the progression of the disease — or even cure it. "Within my lifetime," she says, "a disease has been described, the gene has been identified, and probably before I retire I'll see a definitive therapy for this disorder. That is an amazing thing." ●

Michael Brenner and Felicia B. Axelrod, M.D.

By Rita Baron-Faust

Aspiring to Understand Matters of the FilipinoHeart

WHEN ALLEN LOPEZ (not his real name) was in his 20s, he would not have appeared to be a prime candidate for heart disease. He was fit, trim, and physically active, without any apparent cardiac risk factors — except for one: Lopez is a Filipino American. According to the National Heart, Lung, and Blood Institute (NHLBI), Filipino Americans, like other transplanted South Asians, are three to five times more likely than the overall U.S. population to die from heart attacks and cardiovascular disease (CVD). One reason is an unusually high prevalence of hypertension, at rates that meet or exceed that of other ethnic or racial groups.

Lopez immigrated to the U.S. at age seven from the Philippines. His father, who is hypertensive, suffered two heart attacks before age 50. Despite knowing his family history and being vigilant about his own health, Lopez developed hypertension by his 30s. Last year, at age 39, he underwent a quadruple bypass.

"The risk is more than in our genes; it's our culture," says Lopez. "Filipino culture centers around food, lots of meat, everything fried and loaded with salt. Most of the men smoke and drink, and very few exercise. Because of my dad, I always thought heart disease was inevitable for me."

Lopez now works as a strategic consultant for Project AsPIRE (Asian American Partnerships in Research and Empowerment), a unique alliance between NYU researchers and a coalition of community-based organizations in two Filipino American communities. Led by NYU's Center for the Study of Asian American Health, Project AsPIRE is the first comprehensive study of CVD among Filipino Americans.

"Native Filipinos not only have the highest rates of hypertension among ethnic groups but also develop CVD at younger ages and at a lower BMI (body mass index), 20–21, well below the cut-off of 30 for obesity," says Project AsPIRE's lead investigator, Mariano J. Rey, M.D., director of the NYU Institute for Community Health and Research and senior associate dean for community health.

Rates of hypertension and CVD soar once Filipinos immigrate to the U.S., with lifestyle and social factors aggravating genetic risks. Filipinos may have a genetic defect that prevents proper excretion of salt by the kidneys, he explains, and Asians as a whole tend to develop abdominal fat even at lower BMIs. "But there has been very little published research," says Dr. Rey, who is also director of the Cardiovascular Rehabilitation and Prevention Center.

Funded by an 11-year grant from the NIH, Project AsPIRE is studying the physiologic risk factors — as well as lifestyle, cultural, and social factors (such as immigration stress and job discrimination) — that may contribute to high blood pressure and early CVD in two Filipino American communities (Elmhurst, NY, and Jersey City, NJ). Project AsPIRE will also direct a three-year clinical trial of educational interventions conducted by community health workers to improve management of hypertension. More than 500 hypertensive men and women will be randomly selected for the trial.

The more intensive intervention will require follow-up home visits, referrals to primary-care physicians, and support for compliance with antihypertensive medication.

The Filipino American community is insular, however, and full participation is needed to ensure the success of such community-based research. NYU was instrumental in forming the Kalusugan Coalition (KC), composed of faith-based, civic, government, and community organizations. The coalition (*Kalusugan* means "health" in Tagalog, a main Filipino language) is helping to facilitate recruitment for the study and aid outreach efforts. The KC is also helping to identify local healthcare providers and sites for health-screening events, says Rhodora Ursua, M.P.H., director of Project AsPIRE. "We have a true partnership between an academic institution and the community that we hope will result in some groundbreaking research," says Ursua. ●

Excellence in Community Health

The NYU Institute for Community Health and Research was created in 2006 to address and remedy the health disparities within New York City's minority communities. The institute has four centers dedicated to translational research: The Center for the Study of Asian American Health; the Center for the Health of the African Diaspora; the Center for Latino Health; and the Center for Health and Human Rights. The institute has been designated by the National Institutes of Health (NIH) as a National Research Center of Excellence and by the Centers for Disease Control and Prevention (CDC) as a National Center of Excellence to Eliminate Health Disparities. NIH and CDC grants to the institute and its centers total $25 million, with an additional $10 million in grants from New York City and New York state. ●

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