

Mirpur's Children



A SLUM IN BANGLADESH YIELDS CLUES ABOUT IMMUNITY, INFECTION AND AN ILLNESS THAT AFFLICTS MILLIONS WORLDWIDE. BY DAVID JARMUL



PAVEL RAHMAN / AP

Rashidul Haque steps over a gutter filled with human waste as he visits a neighborhood that holds answers to scientific mysteries about infection and immunity. The bamboo homes in this Bangladeshi slum are pressed so close together that light barely penetrates. In tiny rooms, children work at wooden looms. Water drips from corrugated roofs onto goats, broken bricks and mud. Music blares from a nearby bazaar.

A woman stops Haque to discuss her daughter, one of 235 children he is monitoring to learn about amebiasis, a parasitic disease that each year causes about 50 million illnesses and up to 100,000 deaths worldwide. Haque is an *hhmi* international research scholar who heads the parasitology lab at the Center for Health and Population Research in Dhaka, Bangladesh's capital city.

Haque and the anxious mother review the familiar questions. Does the child have diarrhea? For how long? Is there blood in her stool? Haque's colleague, Lutfar Rahman, who accompanies him on these weekly tours and lives in a house around the corner, arranges for the girl to receive free treatment.

Hasna. Sultana. Amir. Rafique. Kalim. They are the children of Mirpur, one of many such neighborhoods in Dhaka, and they get amebiasis at an alarming rate. In some children, infection from the parasite *Entamoeba histolytica* does not necessarily lead to illness, and when illness does occur, it tends to be less acute than other diarrheal diseases such as cholera and rotavirus. In children and adults of poor families who are already malnourished, however, the bug can sap strength and cause liver abscesses.

Haque has been studying the children of Mirpur for several years and recently published what a reviewer for *The Journal of Infectious Diseases* called "critical insights" into why some become infected more than others. Combining epidemiology with molecular biology, Haque showed that children with antibodies to *E. histolytica* in the mucous lining of their digestive tracts were less likely to become re-infected (see figure, page 25). Their immunity was only partial and short-lived, but the fact that it existed and was mediated by antibodies in the gut—rather than in the bloodstream—caught the attention of amebiasis researchers and others interested in the underlying science of how deadly parasites infect the children of the developing world.

"Until recently, scientists were using traditional techniques like microscopy to study parasitic diseases," says David Sack, a Johns Hop-

Dhaka, the capital city of Bangladesh, is home to 10 million people. Researchers are studying deadly childhood infections in Mirpur, one of Dhaka's overcrowded neighborhoods.

kins University researcher who directs the Dhaka center. "Now, with new molecular tools, we're in a position to make real progress. It's essential that we not limit these tools to places like Hopkins, Harvard and Stanford, where you don't get the reality check of patients coming through the door with these diseases every day."

Haque gets his daily reality check as he walks up to his office. Beside the stairs are rows of beds from the Center's hospital, still known locally as "the cholera hospital." The beds have mattresses with holes in their centers for patients too weak to rise during bouts of diarrhea.

The children's wards are the most crowded, filled with mothers who dab at their children's bottoms with pieces of saris and feed them water mixed with sugar and salts. Last year, the Bill & Melinda Gates Foundation presented its first \$1 million global health award to the Center for its role in developing oral rehydration therapy, which has saved countless lives in Bangladesh and elsewhere.

Upstairs, in Haque's laboratory, a poster displays "eggs and larvae found in faeces." A tray holds test tubes with saliva samples from the children, which Haque's team will test for antibodies. Inside a drawer are the latest stool samples, to be tested with an assay that Haque helped develop to distinguish between *E. histolytica* and *E. dispar*, a nonpathogenic infection that looks identical under the microscope. About two decades ago, the discovery that there are genetically distinct varieties of the parasite cast doubt on the validity of much of the previous research on amebiasis.



Rashidul Haque monitors children for amebiasis. His center provides free medical treatment.

Haque's laboratory has curiosities such as a huge jar filled with 2,269 *Ascaris lumbricoides* worms gathered from 114 people, but it lacks expensive equipment such as the fluorescence-activated device he'd like that would speed the sorting of different cell types from samples. Still, Haque has been able to probe how T cells, B cells and other players in the immune system respond when parasites invade.

"Recently, I've been focusing on the cellular immune response,

Meanwhile, in West Africa ...

While Rashidul Haque carries out research in the slums of Bangladesh, Jan ter Meulen has been facing different problems in the small West African nation of Guinea. An attack by rebels from neighboring Sierra Leone forced many of ter Meulen's staff members to flee their town. Even now, with calm restored, refugee camps are filled with people whose arms were chopped off.

Ter Meulen, a German citizen and HHMI international research scholar, says the turmoil adds to the "tremendous logistical problems" he already faces in his studies of the human immune response to Lassa virus. This virus infects an estimated half-million people in the region annually, causing everything from flu symptoms to death. One in six patients suffers permanent hearing loss from Lassa fever, which is a cousin to other viral hemorrhagic fevers such as Ebola.

"Almost everything has to be imported for our research," ter Meulen explains, who adds that

refrigeration is erratic, roads are unpaved and educated workers are scarce. Not long ago, electricity spikes destroyed two sophisticated PCR (polymerase chain reaction) machines.

Yet, because Lassa fever occurs only in West Africa, ter Meulen remains in the Guinean capital, Conakry, returning to Germany occasionally to carry out more sophisticated experiments at his home base, the University of Marburg. His research is thriving as he uses new biological techniques to reveal how the human immune system recognizes and fights Lassa fever at the molecular level, work he hopes will lead to a recombinant vaccine.

"I have the unique opportunity to bring together field work and state-of-the-art molecular biology," he says. "The work in Conakry gives me access to patients who survived Lassa, which is a great advantage over studying the disease in animal models."

Fellow scientists in Germany and other developed countries often regard his work as "strange and exotic," ter Meulen acknowledges. "It's nearly impossible to build a career as a young scien-

tist on field research on tropical diseases unless you already have a permanent position. Few scientific institutions are interested in researchers working on 'exotic' diseases, except if there are interesting molecular aspects. Money for applied research is hard to get because the diseases do not play a role in the Western world, and the affected countries have no buying power."

But ter Meulen has no plans to leave his tropical laboratory. He says he is intrigued by his work and grateful for the perspective that his stay in Africa has given him. Moreover, his commitment is paying off. One of his recent scientific papers, in the March 2000 *Journal of Virology*, described for the first time how human T cells respond to Lassa virus. And lately, ter Meulen has been receiving repeated invitations to "give talks on my exotic subject."

"I've always enjoyed traveling and working in a developing country," he says, "and I'm lucky that the woman I've been together with for almost seven years also doesn't want to settle down. We both enjoy the freedom and privilege of being able to regularly change our environment and our perspectives." —DJ

Finding Their Niche

How can biomedical scientists in countries with limited resources compete against their counterparts at large, well-equipped laboratories in places such as the United States? Rashidul Haque in Bangladesh and Jan ter Meulen in West Africa have taken advantage of their locations by focusing on diseases—amebiasis and Lassa fever—that are prevalent locally but uncommon in the West. Other scientists whom HHMI has funded around the world have adopted different strategies.

Near Mexico City, Carmen Clapp is making the most of her environs as she pursues one of biology's hottest topics. A researcher at the National Autonomous University of Mexico, Clapp is studying a protein involved in angiogenesis, the process of blood vessel formation

that has fascinated several prominent cancer researchers in recent years. Clapp derives the protein from tissue, provided by local eye surgeons, from children with premature retinopathy. "In more developed nations, doctors use laser surgery, so these samples can rarely be obtained," Clapp says.

Krisztina Kovács at the Hungarian Academy of Sciences in Budapest has found a comparatively quiet niche at the intersection of immunology and neuroscience. Her lab studies how allergies affect the central nervous system, a topic she says "nobody cares much about" despite its intellectual vitality and potential clinical importance. "It's a new field and very interesting, but it's completely neglected," she explains.

Scientists in distant locales have a range of views about how to select a research topic. "It

depends in part on your personality," says Grzegorz Hess, a neuroscientist at Jagiellonian University in Kraków, Poland, whose research techniques "don't require a constant flow of resources." Ivan Shatsky of Russia, for one, says "if you can't compete, it's not worth bothering." A researcher at the A. N. Belozersky Institute of Physico-Chemical Biology at Moscow State University, Shatsky says "you should try your own original way, but it should be interesting. To just repeat someone else's results is stupid."

Ultimately, many scientists around the world say they're guided more by their own interest in a topic than by calculated career strategies. "In the end, you need to be happy," says Fernando Lopez-Casillas of the National Autonomous University of Mexico. "You can't just work on something because a pile of money will be there." —DJ

which involves the T cells," he explains. "We're hoping to begin some new kinds of genetic analysis, since there has to be a reason why some children get infected more easily than others, and why only a few get sick while most are asymptomatic. Their genes may play a role."

Haque's collaborator, William Petri, Jr., of the University of Virginia, has identified and characterized the part of the parasite that latches onto human cells, and demonstrated that the attachment sets off intracellular signals that cause the cells to commit suicide. Working in vastly different settings, the two men have become close friends, communicating daily by e-mail and meeting at each other's laboratories, although Haque jokes that he still cannot persuade Petri to eat spicy Bengali cuisine.

"Sometimes when you have a collaboration, you give more than you get," Petri says. "It's been just the opposite for me. This is definitely not a program that's intellectually driven from the United States." Petri notes that it was Haque who suggested they check the children for antibodies in their digestive tracts as well as their blood. "It didn't occur to me to test for an immune response in the stool," Petri recalls, "but Rashidul was familiar with the cholera literature and thought we should do it."

Both men say their goal is to develop a vaccine for amebiasis, which afflicts people throughout the world. "Understanding the natural history and immune response to amebiasis is essential," says Petri, who has begun talking with companies about such an effort. Vaccine developers may well seek to mimic the immune response that Haque and the others discovered in the gut, but

they'll need to boost this protection and make it last longer—and provide it cheaply to children in places like Mirpur.

Walking through the slum during his weekly visit, Haque reflects on the special problems he faces carrying out biomedical research, which he began pursuing as a doctoral student in Bulgaria. During this two-hour visit to Mirpur, the power has gone out three times, the water stopped and a political demonstration blocked the roads. Haque is also concerned about the delivery of supplies from abroad and about his three-year-old daughter, who just got diarrhea after eating at a fast-food shop.

Still, he remains focused—and remarkably optimistic. "There are very few of us working on amebiasis around the world," he says. "It doesn't get as much attention as a lot of diseases that affect fewer people, but with all of these new tools, we really are making progress."

Petri concurs, emphasizing that high-tech research into everything from the molecular structure of the antigen to the genetic variations among both people and parasites must be accompanied by studies in places like Mirpur. "If you're doing laboratory research, you need to see if your ideas will work in the real world," he says. "I couldn't possibly do the kind of study that Rashidul is doing, even if I was there every day. His team knows the people and can relate to them. They provide them with free medical care. If it weren't for them, we'd have no idea whether the research we're doing here in the States makes sense." ■

Immune Resistance to Amebiasis

Rashidul Haque found that children with antibodies to the *E. histolytica* parasite in their digestive tracts [IgA(+)] were less likely to become reinfected than children without antibodies [IgA(-)] in the gut. To make a difference, the antibodies had to be found in the gut, not the bloodstream.

