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Edited by Jane Alexander

NATIONAL SCIENCE FOUNDATION
Division of International Programs

The National Science Foundation wishes to thank all the STI participating scientists who contributed their time to describe their work and provide photographs. In addition to the collaborating scientists in the United States and in India, several people were especially helpful in developing this report. Ms. Mildred Bolilevac of NSF facilitated the editor and writers' use of all technical reports of on-going research and liaison with Program Managers in STI Government Agencies. Ms. Elizabeth Tait provided White House photographs. Dr. A. Meer and Mr. S.K. Dutt of the Science Office of the American Embassy in Delhi assisted science writers in travel arrangements for interviews throughout India. Dr. U. Trivedi, Director of STI in the Indian Department of Science and Technology, assisted in rapid clearances for science writers and helpful suggestions on this NSF publication.

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"New technologies will provide solutions to maladies [that] today seem insurmountable. Free people, free minds and free markets will [ensure] a more prosperous and peaceful tomorrow."

Ronald Reagan.

"We have so much in common—so many ideals, so many visions of the world—let us work together to make a better world for everyone to live in."

Rajiv Gandhi

Foreword

The presidential Science and Technology Initiative with India is a highly successful example of a new approach to scientific cooperation, and a model for future agreements with other countries. Several design features have been crucial to its success. First, the program focuses on areas where both countries participate as scientific equals, with joint investment of resources for mutual benefit. Second, endorsement of the Initiative by the President and Prime Minister, respectively, of the two countries has given high visibility to the research activities and streamlined the administrative procedures. Finally, the high level support has enabled the Initiative, with minimal expenditure of funds, to draw on some of the best scientific and engineering talent in both countries. The fruits of this cooperation between the United States and India are expected to benefit not only the two partners but many other countries as well.

The Initiative has been a pioneering effort. It is our hope that it will now be viewed as a precedent.

William R. Graham

William R. Graham
Science Advisor to the President

November 1, 1986

The Top Down Approach to Mobilizing Talent

A mutually beneficial collaboration has attracted top researchers from both India and the United States and provides a model for partnerships elsewhere.

by Jane Alexander

When President Ronald Reagan and Prime Minister Indira Gandhi launched the Indo-United States Science and Technology Initiative, STI, on July 29, 1982, they envisioned the new project as a way of reinforcing mutual interests and bringing their two great democracies closer together. "We had a lot of common values and similar desires to resolve differences that had cropped up over the years," says Harry Barnes, then Ambassador to India. "An obvious means of improving relations was to capitalize on our long and productive history of scientific and technological collaboration."

Science and technology were so clearly the right implements to bring about harmony. Both leaders saw a challenging collaboration as a way to improve economic progress and the health and well-being of their diverse peoples.

According to Nyle C. Brady, Senior Assistant Administrator for Science and Technology in the Agency for International Development and an early architect of the Initiative, STI would help give recognition to the scientific stature that India has achieved over the past generation and would also give impetus to both nations to apply their scientific talent toward solutions that would accelerate economic development in other countries around the world.

"Particularly exciting," says Ahmed Meer, American science counselor to India, "was the idea that when our people benefit, so will all the world's people." And when the world's people prosper, so will ours, for our national interest depends in part on a content and prosperous world.

Like her father Jawaharlal Nehru, Prime Minister Gandhi had a deep faith in the power of science to improve the lot of the Indian people. Science, said Nehru, "is based on a fearless search for truth, on the solidarity of man, even on the divinity of everything living and on the free and cooperative development of the individual and the species, even to greater freedom and higher stages of human growth."

More than 13,000 Indians are currently studying in American universities, most in fields of science and technology. Two recent American Nobel laureates are of Indian origin. "India is about to do with the technological revolution what she has already done with the green revolution," says Vice President George Bush.

The aim of STI is to build on these strong points. From the outset, both leaders envisioned a unique program—one that would have their total commitment. In other Indo-United States collaborations over the years, the inspiration has generally come from the bottom up: two scientists with mutual interest agree to work together. By contrast, the motivating forces in the new Initiative work from the top down. The direct interest and involvement of the President and the Prime Minister would efficiently and quickly cut through the layers of bureaucracy and red tape that often stall projects for months, even years, freeing working scientists to generate ideas without interference.

Moreover, the program was to differ from most joint ventures of the past in being a true collaboration, one based on

The Senior Scientific Panel, led by D. Allan Bromley on the American side and S. Varadarajan on the Indian side, met in India in January, 1983, to work out the ground rules for STI. From left to right Henry Ehrenreich, T. N. Khoshoo, Robert H. Burris, D. Lal, D. Allan Bromley, S. Varadarajan, Norman E. Borlaug, O. P. Gautam, Richard M. Krause, V. Ramalingaswami, and Harry G. Barnes, then ambassador to India. Not shown are E. C. Subbarao and Robert M. White.

"Carefully selected and well-managed programs of cooperative work in science . . . can build true links of understanding. The persons involved speak a common language of science. Shared experience can bring succor to millions all over the world."

Indira Gandhi

reciprocity. "Each country was to be an equal participant—investment partners, if you will—with neither side patronizing nor dictating to the other," says Roger Doyon, who heads up the Executive Agent's office of Indo-United States Science and Technology Initiative within the National Science Foundation.

Past technical aid programs have often incurred resentment on the part of recipients because of what they perceive as patronizing attitudes—the missionary approach. The partners were to be equal in every sense of the word, and areas of cooperation would be chosen so that each party could genuinely benefit. The Initiative would provide links and communication channels that would bring the two peoples closer. "By matching scientists at home and overseas, combining equipment and brains, networking, the physical presence of Americans in India is not necessary," says Jake Halliday, director of Battelle-Kettering Laboratory, an STI participant.

The leaders articulated an overall policy, calling upon the expertise of prestigious scientific institutions in both countries. They hoped thereby to ensure the participation of eminent scientists and engineers, the people who command their fields and lead others.

Work on STI began in earnest in November, 1982, when George Keyworth, director of the Office of Science and Technology Policy and scientific adviser to the President, led a high-level policy group to India to define the major areas of collaboration. Together with his counterpart, M.G.K. Menon, chairman of the Science Advisory Committee to the Cabinet, they explored four areas of interest, which Reagan and Gandhi had already discussed: health, agriculture, meteorology, and photovoltaics.

One of the members of the United States group, D. Allan Bromley, Henry Ford II professor of physics at Yale University and President of the American Association for the Advancement of Science, was impressed by the enthusiasm of the Indian Prime Minister. Though she had no formal training in science—and though a political crisis was brewing in one of the Indian provinces—she took time out to attend meetings and ask penetrating and cogent questions.

"Each country was to be an equal participant—investment partners, if you will—with neither side patronizing nor dictating to the other."

One of the group's tasks was to work out the ground rules for the Initiative. They decided, for example, that both countries must have proven expertise in the areas chosen; each area must have demonstrated a need for additional research; and each must promise tangible short-term payoffs while also showing a need for long-term collaboration.

"In other words," says Deborah Wince, Assistant Director of the White House Office of Science and Technology Policy, "we wanted to derive fundamental new knowledge, as science is supposed to do, but we wanted social and economic payoffs as well."

Despite these stringent ground rules, the problem turned out not to be finding projects but deciding which ones to leave out. At Keyworth's request, Bromley put together a Senior Scientific Panel, consisting of six eminent American scientists knowledgeable in the areas the President and the Prime Minister had identified. His Indian counterpart, S. Varadarajan, then Secretary of the Department of Science and Technology, put together a similar panel of Indian scientists.

From January 24 to 31, 1983, the American panel met in India for round-the-clock discussions based on working papers they had put together with the help of leading scientists back home. Whenever someone tried to delay or pass the buck, Bromley was quick to invoke the name of the President or the Prime Minister. "But you don't understand," he liked to say, "our leaders want this program." It was amazing, he says, how quickly people fell into line.

"By mid-week, we had all our proposals together, and I stayed up all night writing a draft protocol in long hand," says Bromley. "I spelled out all the things we wanted and included many bits and pieces of technical

S. Varadarajan, leader of the Indian Senior Scientific Panel, and his American counterpart Allan Bromley take a break from round-the-clock discussions on STI.

detail. When we came into the meeting the next morning, I think the Indians were surprised. We had the basis for real negotiations. And the criteria were extremely tough. Neither side would give ground on some issues. For example, we had the capability of doing a model of weather over tropical oceans, which could help the Indians predict monsoons. But we wouldn't agree to that unless the Indians gave us a large body of Indian Ocean satellite data, which would make our climatic models realistic. Eventually we agreed."

The range of suitable projects was so enormous, Bromley says, that the panel had to turn down some interesting ideas. One, for example, concerned water buffalo, animals of economic significance in India. Water buffalo are extremely phlegmatic beasts. A male can't even tell when a female is fertile, for example, making reproduction a chancy enterprise. If science could help nature along, it might be possible to increase the water buffalo population, thus helping regional economies prosper. But it was hard to see how such a project would benefit both nations.

The next day Indira Gandhi signed the document. "We had negotiated a strong protocol," says Bromley, "and we all breathed a great sigh of relief. Both sides were sensitive to the political nature of the problems. There was a tremendous spirit of camaraderie. We were all privileged to take part in something new that would make a real impact on our countries."

On March 18, George Keyworth announced the four proposed research areas, and the Science and Technology Initiative was officially launched. In making the announcement, Keyworth, said, "The Scientific Panel's success in producing detailed recommendations in such a short time indicates the spirit of cooperation that characterizes this new endeavor. I'm sure their success was speeded by the fact that the research will be truly collaborative, with balanced participation by scientists from both countries."

The area of most pressing concern was health. Despite enormous progress against debilitating and fatal diseases over the last half century, infectious disease is still the main cause of sickness and death throughout the world. The panel outlined three promising avenues to pursue. One proposed to apply immunology to the diagnosis and cure of infectious disease. Another would apply immunology to the problems of infertility and contraception, and the third would attempt to prevent blindness caused by certain diseases and nutritional deficiencies.

In agriculture, an area in which India and the United States had long cooperated, the Senior Scientific Panel zeroed in on nitrogen, an element essential to all life. If we can learn how to improve the ability of certain organisms to fix nitrogen, that is

"STI quickens the pace of science for researchers and speeds the approval of new research projects, allowing scientists to start projects while their enthusiasm is still high."

make it suitable for plants to use, we could change the way we do agriculture, significantly lower costs, and feed the world's hungry. Making better use of the nitrogen in fertilizer will also speed this objective. In addition, STI agricultural research would try to improve reforestation techniques to provide renewable energy sources for rural populations, improve soil conditions for agriculture, and control floods.

Better prediction of monsoons, both short term and long range, is a matter of vital concern to India. And because the monsoon affects the weather around the globe, it concerns the United States as well. In recent years, for example, meteorologists have discovered that poor monsoons in India and abnormal weather in the Eastern Pacific may be linked to common causes—and that one may predict the other.

Finally, the panel recommended research into new technologies of photovoltaics, materials capable of converting sunlight into electricity. Cheaper photovoltaic cells could bring light, irrigation pumps, educational television, and refrigeration for the storage of medicines to millions of people who have no access to central power systems.

Before work could begin, Indian and American scientists had to convene workshops to refine each project. Proposals were submitted for peer review in each country and finally modified by bilateral discussions. As the Executive Agents for the program, the National Science Foundation in the United States and the Department of Science and Technology in India oversee and coordinate the individual activities. In the United States, for example, Roger Doyon of the National Science Foundation, coordinates the effort of various government agencies that manage the individual programs.

Because of the high visibility of the program within the two governments—the top-down approach—the United States agencies are involved partners. Burdened as it has traditionally been with cumbersome grant-approving mechanisms, the Indian government has installed novel mechanisms to handle STI. A special administrative cell within the Department of Science and Technology, staffed mainly by scientists and headed by U.C. Trivedi, expedites approvals of research projects under the STI program, as well as scientists' visits and their training and access to information, equipment, and materials.

A distinctive feature of STI is independent scientific overview. The United States National Academy of Sciences' National Research Council cooperates with a corresponding Indian Senior Scientific Panel to produce periodic reviews that ensure things are working as they are supposed to, point out areas of concern, and suggest programs that might be added or dropped.

William Gordon, chairman of the National Research Council's overview committee says the early returns from STI have been extremely positive. "It has made it easy for India and the U.S. to collaborate," says Gordon. "As one Indian said to me, 'It's as easy now to work with someone at the National Institutes of Health as it is to cooperate with someone down the hall.' It is a good example of how a small bilateral project can have significant impact toward achieving the goals of both our countries."

"Investigator to investigator research is the best kind and that's what STI is all about," says Linda Vogel, Associate Director of the Office of International Health at the Public Health Service.

Jean Johnson of the STI Program Office at the National Science Foundation, agrees. "STI quickens the pace of science for researchers and speeds the approval of new research projects," she says, "allowing scientists to start projects while their enthusiasm is still high, something that can't always be said for governmental projects. Scientists like being part of a whole group of interrelated projects, like those on immunology, for example, rather than working on one isolated project. The kind of intellectual stimulation this has engendered has been a great drawing card attracting the very best scientists to work in the STI."

"It's been a very fruitful experience from our side," says S. Ramachandran, then Acting Secretary of India's Department of Science and Technology. "We've learned to move things along the fast path instead of through the bureaucratic maze. Many of our senior scientists say they'd like to get involved in STI, even if no extra money is involved." Indian scientists out in the field generally concur. Many particularly relish the opportunities STI affords to work with American counterparts, either in each others' labs or in various workshop conferences that are periodically held in either country.

The same themes come up again and again—how collaboration increases understanding between scientists of different countries and makes it possible to do things together neither country could do alone and how the high-level attention to the project has speeded the normal pace of research, encouraging many scientists to work on the project who might not have otherwise, seeding new ideas that are bringing about exciting findings.

On June 12, 1985, during Prime Minister Rajiv Gandhi's trip to the United States, he and President Reagan extended STI until October, 1988. STI now includes some 70 research projects in four areas involving more than 100 researchers in the United States and a similar number in India. About 25 scientists in each area travel back and forth each year. The United States spends approximately $7,000,000 a year on the Initiative.

Of the four programs—health, agriculture, monsoons, and photovoltaics—the greatest gains so far have come in health. Because India and the United States had been cooperating in the biomedical area for decades, programs were already in place to build upon. Moreover, there is a reservoir of disease in India that we cannot study here. In exchange, we can bring to India the latest in genetic engineering techniques, technology, and equipment.

Under the coordination of Karl Western at the National Institute of Allergy and Infectious Diseases at the National Institutes

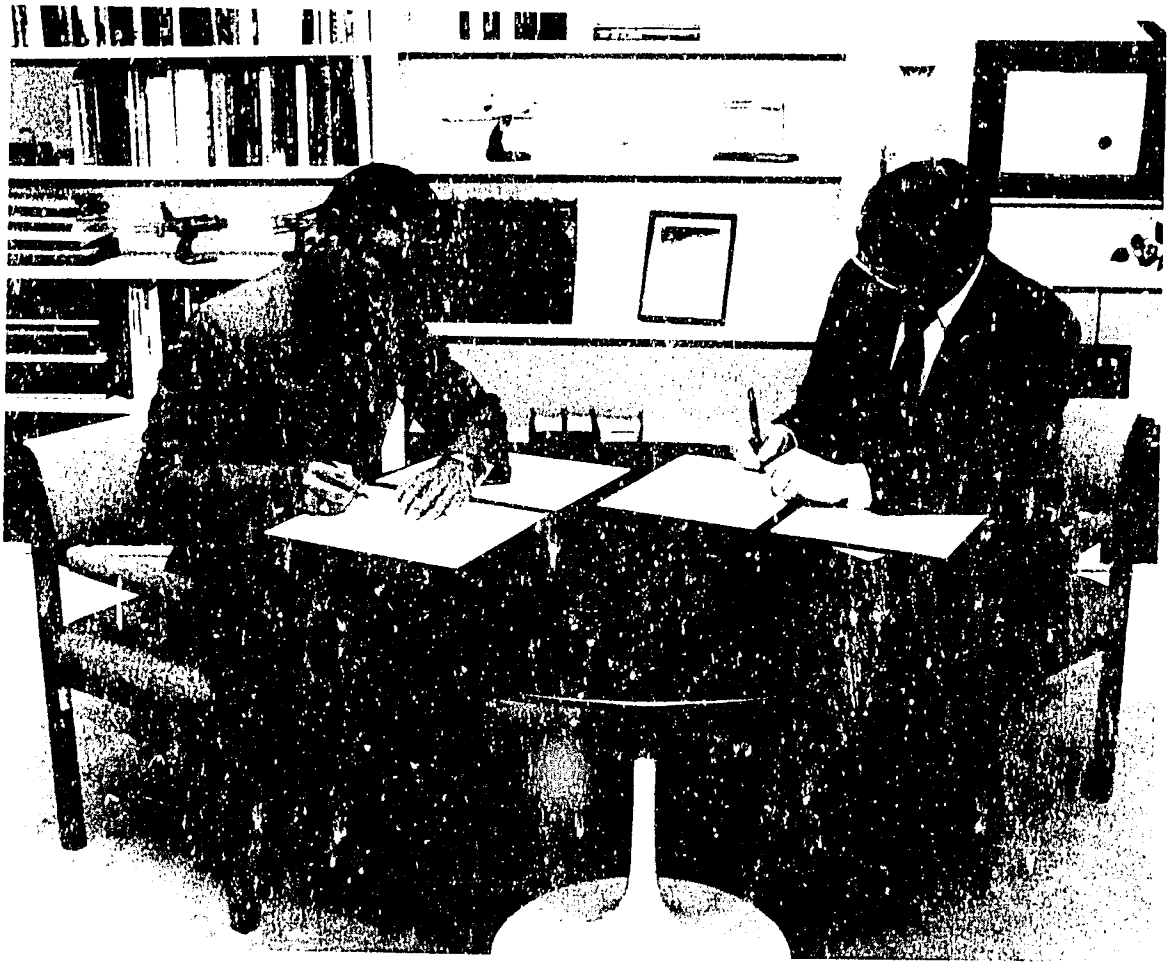
"If you put your reserves to work, you can do a great deal with very little. We already know how to ameliorate blindness in the developing world, so extensive basic research is unnecessary."

of Health, American and Indian researchers are trying to harness recent breakthroughs in the science of immunology to deepen our understanding of disease. Insights from immunology are helping STI teams develop a simple, early diagnostic test for tuberculosis, make progress toward the first vaccine against a parasitic disease, malaria, and improve understanding of the immune system's role in leprosy and filariasis.

Leprosy, a disease mired in social stigma and fear with roots at least as old as the Bible, has been particularly difficult for United States scientists to study. The causal organism, *Mycobacterium leprae,* naturally infects only two animals in the world—human beings and the nine-banded armadillo. The organism refuses to grow in culture. It reproduces slowly and resides in the body without showing symptoms for as long as 10 years.

Given all that, it's obvious that India's four million leprosy cases offer prospects for a casebook collaboration. For Gilla Kaplan at the Rockefeller University in New York City, the project provides insights into the way the disease affects the immune system. There are only a few hundred leprosy patients in New York, and since they have been treated for a long time, it is difficult to learn very much about the nature of the immune response from them.

The disease ranges from the milder tuberculoid form in which the immune system is pretty much intact to the lepromatous kind in which there is little or no immune response to the leprosy bacillus. Even in the latter, though, patients show a normal immune response to other invaders, such as tuberculosis bacteria. Kaplan and others in Zanvil Cohn's lab are collaborating with Indira Nath's group at the All India Institute of Medical Sciences in New Delhi to investigate how and why the immune system



On June 12, 1985, presidential science advisor G. A. Keyworth II and Indian science minister Shri Shivrha Patil sign a three-year extension of STI.

works well in response to one disease but not to another.

"After injecting tuberculosis vaccine into leprosy skin lesions, we biopsy the lesions to find out what T cells [disease-fighting white cells] are doing, what new cells come in and in what sequence," says Kaplan. "We are measuring the immune response in this disease for the first time. This wouldn't be possible without the Indian subcontinent where we have a large number of patients and are able to cover the whole range of the disease. It is all very important because it could aid attempts to create a vaccine against leprosy.

"We work with a group of extraordinarily good scientists in Indira Nath's lab," says Kaplan. "We have access to patients in three different clinics in Delhi, so we can make maximum use of our time there. What we are doing wouldn't be possible without the patients' help. Almost every one of the 100 people we have seen comes back when we ask, and they have to return at least twice for blood tests and skin biopsies. They know it isn't necessary for their health to return, and yet they comply."

STI researchers are also investigating whether the immune system is implicated in certain kinds of blindness. For example, Eales' disease, which impairs vision in one to two percent of the men in India during the most productive period of their lives, resembles diabetic retinopathy, a major cause of blindness in young people in the United States. Both diseases attack the blood vessels in the retina, causing them to multiply, leak blood, and cloud vision. Some suggest that both diseases represent a malfunction of the immune system.

In what appears to be the beginning of a long, slow search, V. Muthukkaruppan at Madurai Kamaraj University is comparing the blood of Eales' disease patients with that of healthy people to see if there is any difference between them—any evidence, for instance of the immune system turning against its own blood vessels.

"If you put your reserves to work, you can do a great deal with very little," says Barbara Underwood of the National Eye Institute, who with Carl Kupfer, the Institute's chief, manages the STI blindness program. "We already know how to ameliorate blindness in the developing world, so extensive basic research is unnecessary. All

Karl A. Western of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health manages U.S. participation in the infectious disease program.

Carl Kupfer, chief of the National Eye Institute at the National Institutes of Health, coordinates the blindness program.

Gabriel Bialy at the National Institute of Child Health and Human Development at the National Institutes of Health coordinates the birth control program.

we have to do now is package that knowledge in such a way that the developing world can use it."

STI researchers like Vinodini Reddy at the National Institute of Nutrition in Hyderabad, for example, have found they can reduce children's blindness resulting from measles and diarrhea by giving them Vitamin A in plain water or in a mixture of water, sugar, and salts. This discovery is simple and cheap and should save lives as well as sight.

In New Delhi, Madan Mohan and his colleagues are studying another cause of blindness—cataract, a disease in which the lens of the eye becomes clouded. In India cataract occurs between the ages of 40 and 60, while in the United States, it generally occurs after age 65. If the onset of cataract could be postponed by a decade, both nations would benefit enormously. STI researchers are looking for risk factors—eating habits, exposure to smoke, sunlight, and dust, smoking habits, health, vitamin and trace mineral deficiencies, economic and educational status—that may predispose people to cataract.

Another imaginative application of the new science of immunology focuses on birth control. It took the human race until 1957 to reach a population of three billion, but reaching the second three billion will take only until the end of this century. Ninety percent of the increase will come in developing countries like India. To combat epidemic overpopulation, Indian and American researchers are collaborating on a contraceptive vaccine under the direction of Gabriel Bialy at the National Institute of Child Health and Human Development at the National Institutes of Health.

"This program is a good example of why such collaboration can be considered additive to what each group can do alone," says Sheldon J. Segal of the Rockefeller Foundation and a member of the National Research Council's overview panel. "A team in New York made a vaccine against luteinizing hormone releasing hormone, or LHRH, which in males leads to the production of sperm. Now a team in Delhi is testing it in a large primate center there and may be close to clinical tests in people."

The disadvantage of this method is that it inhibits sex drive and other secondary sex characteristics so replacement androgens would have to substitute. A second approach to a male contraceptive vaccine interferes only with the hormone that regulates sperm production, leaving the sex drive intact. So far, this vaccine has worked in monkeys.

Far in the future may be a female vaccine affecting the zona pellucida, which would block fertilization entirely. The zona is the thick coat surrounding the egg through which the sperm must penetrate to achieve fertilization.

Agriculture, an area in which Americans and Indians have collaborated since the early 1950s, is also yielding some exciting results. "We have the potential to change the way agriculture is done around the world if we could only understand the complex processes that make biological nitrogen fixation possible and apply that knowledge in a practical manner," says Lloyd Frederick, who manages the agriculture project at the United States Agency for International Development.

"The project has just flown along," says Jake Halliday, of Battelle-Kettering, which is involved in nitrogen fixation for STI. "We have been able to do work that is intrinsically fascinating to us, which we couldn't have done without the collaboration. Both countries needed the intellectual input. The United States makes use of the plant material that the Indian scientists share with us, while the Indians take advantage of our techniques and instrumentation. This is a kind of grass roots science that really turns people on."

For example, electron microscopist Harry Calvert recently identified a new symbiotic relationship in a woody shrub, called *Aeschynomene*, which grows as a weed in rice fields. Calvert had discovered a photosynthetic bacterium (one that like higher plants uses the sun's energy to convert carbon dioxide to carbohydrates) living with a nitrogen-fixing bacterium inside nodules on *Aeschynomene*. "This is the first report of a photosynthetic bacterium living inside nodules" says Halliday. "We've found nodules not just in the roots of the shrub but

Lloyd Frederick of the United States Agency for International Development manages the biological nitrogen fixation program.

John Malcolm of the United States Agency for International Development coordinates the nitrogen fertilizer efficiency program.

Stanley L. Krugman of the United States Forest Service manages the biomass program.

also on its stems. Perhaps the photosynthetic bacterium can fix nitrogen too. How did it get in there? It's not a disease. Can we transfer it to other plants? Can we use it with nitrogen-fixing bacteria as a biological fertilizer? How do microbes like this trick plants so they won't be rejected?"

Another effort to improve crop yields is aimed at the aquatic fern, *Azolla,* whose leaves are inhabited by the nitrogen-fixing blue-green alga, *Anabaena azolla.* Rice farmers in Southeast Asia have used the fern for centuries as a green manure to add nitrogen to their rice paddies.

At the University of California at Davis, Bill Rains has discovered that one strain of *Azolla* indigenous to the United States actually secretes ammonia, a nitrogenous fertilizer, into the water in which it grows. "It's like having a little ammonia factory right there in the rice fields," says Rains. Collaborating with S. K. Goyal of the Indian Agricultural Research Institute in New Delhi and S. Kannaiyan of Tamil Nadu University Agricultural University in Coimbatore, Rains has found that the American strain can increase rice yields by as much as 60 percent over Indian *Azolla* strains.

Another way to make agriculture more economical is simply to improve plants' efficiency in utilizing the nitrogen in artificial fertilizer. Rice plants, for example, often recover as little as 20 percent of the available nitrogen in fertilizer. But if researchers could better understand why these losses occur, some like John Malcolm of the United States Agency for International Development who coordinates this program, believe that many of the losses could be prevented, ultimately raising nitrogen efficiency to 70 percent or more.

Already STI scientists have found that applying fertilizer a couple of days before a heavy rain decreases nitrogen losses as does growing rice in continuously flooded paddies. From trading such information, Indian and American scientists eventually hope to discover for given plant species what types and amounts of fertilizer to apply, when to use them, and at what depths.

Every year the world loses an area of forest half the size of California. Most of the losses occur in poor, tropical countries where the main source of energy is firewood. With plenty of cheap labor, India has been in the forefront of those trying to do something about the problem—planting 12.5 million acres a year, primarily in the Himalayas and the arid, overgrazed wasteland that makes up one third of India's total area.

"This is social forestry, a way that people, not industry, can try to improve the quality of life in rural areas by growing trees and shrubs for fuel, food, and fodder," says Stanley Krugman, manager of the biomass program at the United States Forest Service. "It will help control runoff, save water, and reclaim wastelands for agricultural uses." The aims of the program are to identify which trees are best for which climates, to mass produce seedlings, and to discover the most efficient ways of planting them.

Which, for example, of the 500 species of eucalyptus are most suitble for different areas of India? Some say eucalpytus robs the soil of nutrients and lowers the water table. Would poplar be better? It grows straight, tall, fast—and almost anywhere. Under STI, for example, the United States sends poplar specimens to India where cuttings are planted. Some are taking hold in worn out, arid, over-grazed wastelands—environs very different from their native humid American habitats.

The monsoon, which affects the lives of roughly half of mankind, including everyone in India, is the subject of another STI program. "The monsoon is a highly significant feature in the total global circulation," says Robert White, President of the National Academy of Engineering and a member of Bromley's Senior Scientific Panel. "The program grew out of a personal interest of Mrs. Gandhi, who felt it would be a fruitful area of research. It is an excellent example of a perfect fit between the interests of India and the United States."

The monsoon program consists of two subprograms, according to Pamela Stephens at the National Science Foundation, who manages them. One is short- and medium-range forecasting. Collaborative studies involve improving analysis of winds and temperature and pressure measurements

These maps locate the cities in the United States and India where STI researchers are collaborating.

Pamela Stephens of the National Science Foundation manages the monsoon program.

Roger W. Doyon heads the Office of Indo-United States Science and Technology Initiative at the National Science Foundation, the Executive Agent on the American side.

Jean M. Johnson, program manager in the Indo-United States Science and Technology Initiative Program Office at the National Science Foundation.

obtained from radiosondes, satellites, oceanographic vessels, tide gauges, etc. for use in operational numerical prediction models.

"This variability from day to day," says oceanographer Roger Revelle at the University of California at San Diego and a member of the overview panel, "is very important from the standpoint of agriculture, particularly during the first part of the monsoon, when the rains start and stop. Farmers like to plant their crops after the first rain, but if the next rain doesn't come for three or four weeks, the seedlings die. In Program I, we are interested in this short-term variability—the monsoon onset and the interval between the first and second rains."

When the monsoon fails, people starve and economies totter. Long-range forecasts, which might predict such failures a month or even a year ahead are one of the goals of Program II.

Understanding long-range weather patterns, including monsoons, is also of interest to the United States and Latin America because of newly-discovered connections between monsoons and weather in other parts of the world. An example is El Niño, the strange Christmastime warming of the sea surface water off Latin America's Pacific coast. Not only does El Niño wipe out the Peruvian and United States anchovy catch, but it appears to cause storms in some parts of the world and droughts or cold waves in others. By collaborating on computer models and a multitude of basic research projects, STI scientists are beginning to understand the physics connecting El Niño with monsoons, raising hopes that both will become more predictable.

The most difficult area to negotiate, photovoltaics, was also the hardest to get off the ground. So difficult, in fact, that no agreement was reached until March of 1985 when George Keyworth and M.G.K. Menon made another of those high-level decisions that have propelled the STI project. They renamed the program solid state science and engineering and changed the emphasis in photovoltaics from applied to basic research; they also added an ambitious project on minerals engineering.

Encouraged by early successes of the STI, Prime Minister Rajiv Gandhi and President Reagan have already agreed to initiate two new programs. One aims to develop and produce improved vaccines against infectious diseases. The second involves long-term research and technology development efforts in agriculture, forestry, biomedical research, nutrition, family welfare, and industrial research and development.

The United States is also investigating possibilities for collaborative programs with other developing nations modeled on STI. As David Mog, coordinator of the overview committee at the National Research Council, says, "Serving as a model for such attractive new projects, STI may help fulfill many goals the United States can achieve in no other way. By designing cooperative ventures as joint investments, not as aid programs, we treat our partners as equals, while invigorating their science and technology establishments. This encourages the best talent in each country to come forward and combine forces, thus speeding the progress of scientific discovery."

Both India and the United States have long recognized that democracy thrives best in enlightened, reasonably prosperous, and stable societies. Enlightenment and prosperity, in turn, are largely fruits of scientific and technological enterprise, which requires a climate of free communication among equals, not paternalistic relationships that tend to foster both dependency and resentment. If STI and its successors can foster and maintain such a climate, the programs themselves could turn out to be even more important than the scientific breakthroughs made within them.

Jane Alexander is a freelance writer and editor living in Washington, D.C.

A leper waits for handouts on a market street in Banaras, the holy city of India.

New Immunological Weapons Against Ancient Enemies

Recent breakthroughs in immunology aid in the battle against filariasis, leprosy, tuberculosis, and malaria.

by Robert Kanigel

The textbook pictures show only the affected body parts—stump-like legs encrusted with hardened, leathery skin, grotesquely swollen breasts, scrota the size of basketballs—that mark the tropical disease known as filariasis at its worst. But here, in a ward on the fourth floor of the Government General Hospital in Madras, one recalls that attached to those deformities are minds and hearts and dreams of a better life.

One patient, a chef in his twenties, displays his enlarged scrotum and elephantiasis-ridden leg with an eagerness, almost a clinical thoroughness, that might befit a life-long student of the disease. The absence of pathology in the rest of his well-formed body makes the affected organs seem all the more misshapen. Another patient is a school teacher from a village a hundred kilometers outside Madras. He's unmarried—though not, he hastens to explain, because of his disfiguring disease. For many victims, however, diminished marriage prospects are very much part of the disease's social toll.

Filariasis doesn't kill its ten million or so victims worldwide. It subjects them to periodic fevers. It deforms them for life. In some cases, it affects their lungs, leaving them wheezy and weak. But it virtually never kills. And that may be why it hasn't received the attention afforded other, more scientifically fashionable diseases that affect many fewer victims. Within the Indo-United States Science and Technology Initiative, however, researchers who do grapple with filariasis have found a comfortable home.

STI research on filariasis and other infectious diseases is all guided by a single strategy: exploit recent breakthroughs in the science of immunology to tackle problems long resistant to solution by other means. Thus, Indian and American researchers under STI have made contributions to a new vaccine for malaria. They have deepened science's understanding of leprosy. They have made genuine advances in containing filariasis.

And they have employed their powerful new immunological tools to develop a simple diagnostic test for tuberculosis that can spot victims long before their symptoms would normally surface—and long before they've had a chance to spread the disease to others.

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N. Kochupillai, a native of Kerala in southern India, is supposed to be explaining his tuberculosis work under STI. Instead, he launches into a disquisition on his earlier research into goiter, an iodine deficiency disease marked by conspicuous swelling of the thyroid gland. A listener wonders why—but not for long.

Back in 1971, when Kochupillai joined the All-India Institute of Medical Sciences in Delhi, goiter was still being written off as mostly a cosmetic problem. No one, apparently, had noticed that areas of northern India endemic for goiter were just those areas whose populations were often reputed to lack intelligence and drive. Kochupillai found that more than half the adult goiter sufferers also showed thyroxin deficiency,

Zanvil Cohn of New York's Rockefeller Institute (third from left in second row), who heads up the American investigation into leprosy, joins Indira Nath (first row, left) and her colleagues at an STI symposium on the immunology of leprosy, which Nath organized in India early in 1986.

long linked to mental retardation. Developing a simple screening test for thyroxin deficiency in newborns, Kochupillai then found that whereas in the United States, for example, about one baby in 3,000 suffers from thyroxin deficiency, in these goiter-endemic areas of India the figure went as high as one in seven. Alerted, health planners began widespread neonatal screening and supply of iodine supplements.

The lesson Kochupillai drew from the experience animates him to this day: a simple field test that breaks no new scientific ground and represents no particular intellectual breakthrough can, in a developing country like India, pay vast dividends in improving people's lives. It was this lesson, said Kochupillai, winding up his digression, that he hoped now to apply to tuberculosis.

Even in the United States, where the disease is not an urgent public health problem, there were 2,000 deaths from tuberculosis in 1983. In India, some 10 million people suffer from it. Antibiotics can treat the disease. But to have it treated, you've got to know you have it. And it often takes six or eight months, or longer, before your symptoms are serious enough to drive you to a health clinic; by then, you've spread it to others.

Existing methods of diagnosis, such as microscopic search of a sputum sample for *Mycobacterium tuberculosis,* the agent responsible for the disease, don't encourage rapid screening. Besides, sometimes even advanced cases can elude diagnosis altogether. Plainly, a cheap, easy screening test able to spot the disease early and reliably could help retard its spread.

M. tuberculosis betrays its presence in the body through trace substances that are the product of the microbe's various life processes. Immunologically speaking, such substances can function as antigens; that is, they can provoke an immune response by antibodies, exquisitely specific molecules that recognize antigens, link up to them, and mark them for destruction. And any of these trace substances, presumably, could serve as the antigen that an immunonological screening test could be set up to detect.

Such a test is radioimmunoasssay, developed by Rosalyn Yalow, who won a Nobel Prize for its discovery. Between 1975 and 1977, Kochupillai worked in Yalow's lab at the Veteran's Administration Medical Center in the Bronx, New York, where he used RIA as the basis for his thyroxin deficiency test. With RIA, you let a known amount of radioactively labeled antigen compete with various known concentrations of unlabeled antigen for a known amount of antibody. That preliminary data in hand, you repeat the process with a sample of unknown antigen content and work

Working with American collaborators, N. Kochupillai of the All India Institute of Medical Sciences in New Delhi is seeking a rapid and sure test that will diagnose tuberculosis, a disease that afflicts 10 million people in India.

backwards to determine how much antigen it contains.

Kochupillai and his American collaborators under STI, Yalow and Eugene Straus, of the State University of New York Downstate Medical Center in Brooklyn, had previously developed an RIA for tuberculosis. Now they set out to refine it, hoping to enhance the sensitivity of their assay, see to it that it was not fooled by harmless mycobacteria other than tuberculosis, and finally apply it to the diagnosis of patients.

By early 1986, it was ready to hand over to the Tuberculosis Research Center in Madras for field testing (which on a mass basis, Kochupillai has estimated, will cost about four rupees per person, or about 35 cents). It was possible that the particular antigen they'd picked to measure, known as PPD-CT 68, would ultimately fail to provide the specificity and sensitivity needed. "But," says Kochupillai, "if this antigen is not successful, we'll just try another one.

"We're not trying to do any highfalutin' research, like a lot of other people are doing—poorly. I'm not a dreamer at all. My concern is that if we have a problem, as we do with tuberculosis, what can can we do about it?"

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Mycobacterium leprae. Researchers speak of the causative agent of leprosy, which afflicts some 12 million people around the world, with the kind of grudging respect that British admirals in World War II reserved for the German battleship Bismarck—as a diabolical and resourceful enemy with an uncanny ability to elude capture or destruction.

A mycobacterium, as one STI researcher, David Volkman, explains it, is "half way between a bacterium and a fungus." Tuberculosis is also a mycobacterium, as is a more common if less injurious rash sometimes suffered by swimmers. But there end the similarities, and there begin *M. leprae's* maddening peculiarities.

With the exception of the eastern nine-banded armadillo, an obscure species native to the United States, *M. leprae* infects only humans.

A simple field test that breaks no new scientific ground can, in a developing country like India, pay vast dividends in improving people's lives.

Unlike most other microscopic organisms, it can't be grown in culture.

Under even the most favorable of circumstances, *M. leprae* reproduces at a glacially slow rate, typically duplicating about every 12 days, compared to at least every day for most other microorganisms. So the

The permanent clawlike grip of this leper is caused by a bacillus that damages the fatty myelin tissue surrounding the nerve that controls the muscles leading to the hand.

bacillus can lurk in body tissues, never revealing its presence, oh so gradually wreaking its damage, its human host becoming aware of its presence only imperceptibly.

Even so seemingly basic a question as how *M. leprae* enters the body remains shrouded in mystery. Is it the lungs? The skin? The interval between infection and the appearance of the first symptoms is so long—sometimes a year, more likely five or ten—that pinpointing the circumstances of the original infection is like reconstructing a crime years later, when the witnesses are missing or dead.

The first symptom is almost always a numbness in a discete area of slightly raised, depigmented skin. Typically, *M. leprae* insinuates itself in the fatty tissue surrounding nerves. That provokes an inflammatory response, a thickening and swelling that a physician can feel under his or her hand. A frequent victim of the leprosy bacillus is the nerve controlling the muscles leading to the hand, leaving it in a permanent claw-like grip. The loss of fingers that gives the disease its most horrific connotations—and that historically has led, more than leprosy's unjustifiably feared contagiousness, to the segregation of lepers in colonies—also stems from nerve damage.

Leprosy's effects span a by now well-characterized spectrum between two poles, "tuberculoid" and "lepromatous." The first results in nerve damage and loss of fingers, the second to the more grotesque skin lesions. But the differences are most striking under the microscope. There, tuberculoid lesions show an almost complete absence of bacilli, lepromatous lesions a population so enormous that those who have seen them never fail to remark on it. The first group is not highly contagious, the second is. In tuberculoid leprosy, immune response is normal; indeed, much of the nerve damage is caused by it. In lepromatous leprosy, immune response is nonexistent. While antibody production, for example, is normal, the antibodies fail to counter the disease. In fact, *M. leprae* takes up residence in a class of immune cells, macrophages, that would normally destroy them; yet in lepromatous leprosy, the macrophages apparently protect them.

The object of study for leprosy researchers is* H. sapiens *as much as* M. leprae*, because the disease owes many of its peculiarities to idiosyncracies of the human immune system.

In a real sense, then, the object of study for leprosy researchers is *H. sapiens* as much as *M. leprae*, because the disease owes its peculiarities not only to the infectious agent but to idiosyncracies of the human immune system. Indeed, contrary to general perception, leprosy is hard to catch, most people's immune system successfully fighting it off. In southern India, for instance, it's been estimated that only about four per cent of the population are vulnerable. For STI researcher Indira Nath, of the All India Institute of Medical Sciences in New Delhi, leprosy is not just a disease, but "a beautiful model for understanding the immune system."

In a normal immune system, macrophages and dendrites "present" the invader to T-cells which first recognize its surface markings and then, through a complex series of events, order its destruction by other elements of the immune system. In lepromatous leprosy, this system breaks down. T-cells, which continue to respond normally to other invaders, are nowhere to be found. What's going on? Which of all the antigens in *M. leprae* is the one, or ones, to which tuberculoid patients, who do mount a strong immune response, respond—and to which lepromatous patients, who do not, don't? "Maybe," as David Volkman says, "that would be a very good protein to be immune to."

Thus, most STI leprosy research projects represent one or another probe into the disease's poisoned immune reponse. One pair of collaborators, Volkman and Nath, set about cloning antigen-specific T-cell clones—T-cells that recognize only particular molecular segments, or epitopes, of *M. leprae*. Nath, a leading figure in leprosy research who helped organize a much-

A group of researchers at the immunology symposium probe the mysteries of M. leprae, *the infectious organism that causes the dread disease.*

lauded Indo-U.S. Symposium on Immunology and Molecular Biology of Leprosy in early 1986, also collaborated with Zanvil Cohn and his colleagues at New York's Rockefeller University in a study of how macrophage response differs between the lepromatous and tuberculoid forms. In another project, they focused on the antigen-presenting role of a class of cells called dendrites. ("Maybe it's not the T-cells that are defective, but that the antigen-presenting stage is defective," explains Nath.) In a fourth project (of seven), STI researchers sought to synthesize one particular molecular component of *M. leprae*, a "phenolic glycolipid," suspected of undermining normal immune response.

Indira Nath of the All India Institute of Medical Sciences in New Delhi, who leads Indian participation in leprosy research, is trying to find out how the immune response differs in the two forms of the disease.

Today, leprosy can be treated with a number of drugs, such as dapsome and rifampin. But *M. leprae's* ability to lie low, as it were, means that victims must be treated for years—difficult anywhere, much less in a developing country like India. "How, for so long, do you treat people on the street?" asks David Volkman. Besides, even once cured, the victim is just as susceptible as he was in the first place.

And so, beyond a deeper understanding of human immune response, the end goal of leprosy research is a vaccine. Vaccine strategies, as Indira Nath ticks them off, are several. One is to marshal gamma interferon, now available in substantial quantities through recombinant DNA technology, to speed up the killing of bacilli. Another is to use killed leprosy bacilli plus BCG, a product of leprosy's mycobacterial cousin, *M. tuberculosis*, to spark a healthier immune response. A third would be a peptide vaccine synthesized from scratch. "You'd just give the product that triggers the T-cells into action," explains Nath. "That's the dream. That's the really neat way to do it."

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"In filariasis, you've got a criminal living right in the middle of a police station and the cops doing nothing about it," says V. Kumaraswami, an STI researcher with the Tuberculosis Research Center in Madras. The "criminal" is the parasitical worm *Wuchereria bancrofti*, or its cousins. The "cops" are the body's lymph-borne immune defenders. The "police station" represents the lymph nodes from which they fan out to protect the body.

Filariasis unites human, mosquito, and parasite in a complex interdependency. A larva-infected mosquito bites a human. Through the resulting break in the skin, the larva burrows through, finds its human niche, and grows to adulthood. Mating adult worms, often three or four inches long, slough off thousands of microscopic worms known as microfilariae. Inhabiting the blood stream, one of these may later be ingested by another mosquito, into whose thoracic duct it migrates. There, over a period of about a month, it develops through two larval stages before it's ready to find a human home and renew the cycle.

In their human host, filarial worms lodge in the lymphatic system, the network paralleling the blood circulatory system that cleanses the tissues of bacteria and certain proteins. Normally, if you cut your foot, say, lymph nodes in the groin and elsewhere deliver infection-quelling lymphocytes to the site of the injury. In filariasis, the movement is in the opposite direction: A larva of *W.*

This building serves as a regional training and research center for filariasis in Calicut at the southwestern tip of India.

bancrofti entering the body through the foot travels up the lymphatics to a node in, for example, the groin. There it matures into an adult worm. And there it does its damage.

At first, the normal immune response to the worm causes inflammation, fever, and local swelling which, after a week or so, usually subside. But with recurrences, the lymphatics are first scarred, then obstructed. "The pipes clog, the lymphatics don't drain," is how long time filariasis researcher Eric Ottesen, of the National Institute of Allergy and Infectious Diseases, puts it. Fluid backs up, ultimately leading to the grotesquely enlarged legs (sometimes a yard or more in circumference), scrotums (sometimes weighing five or ten pounds), breasts, and other body organs that are filariasis' most visible and unwelcome consequences. (Elephantiasis cannot be reversed, though some plastic surgeons try, sometimes with disfiguring results. In any event, most rural victims can hardly afford the third class train fare needed to reach the surgeon or the time away from work, much less surgeon's fees.)

Like leprosy, filariasis can be treated, with a drug called diethylcarbamazine, or DEC. "The drug makes me sick," is the lament often heard among patients who, prior to treatment, were symptomless. And it's true. STI researcher Robert Hamilton, of the University of Texas School of Medicine in Houston, explains that DEC excites the microfilariae into activity, awakening the immune response that kills them. That reduces the reservoir of baby worms from which mosquitos draw and by which the disease is spread, making DEC an effective public health measure. Whether it also kills adult worms is not as certain.

With any disease, treatment normally follows diagnosis and it's diagnosis that's the sticking point in the case of filariasis. The customary way to check for it is to take a little blood, smear it on a microscope slide, and look for microfilariae. But that method is fraught with a maddening complication—that the microfilariae appear and disappear from the blood in regular cycles. A blood sample of an infected person may appear barren of microfilariae at noon, while one of the same patient 12 hours later may reach concentrations of 10,000 per milliliter. Then, twelve hours after that, the baby worms are gone again. Why the cyclic rise and fall? Where do the microfilariae hide when absent from the blood? "Let me start off by saying," the Tuberculosis Research Center's V. Kumaraswami replies to the question, "that nobody knows." Eric Ottesen pictures the parasites as somehow keying into the natural biological clock of the human body. Robert Hamilton suggests that perhaps they are acutely sensitive to body temperature, which goes up and down cyclically. In any case, microfilariae concentrations do vary wildly through the day, with filarial species seen in India, for example, reaching a maximum at about two o'clock in the morning. Which means that a health worker wishing to screen villagers for the disease had better be out there knocking on doors long past midnight.

"Night bloods," this customary middle-of-the-night screening is called. It imposes immense logistical hardships. And it fails to detect certain phases of the disease at all. Indeed, it is so much the bane of health care workers that, short of a vaccine to prevent the disease altogether, no goal is more sought among filariasis researchers than a simple, cheap, and reliable screening test to replace it.

Until recently, efforts to diagnose filariasis took an indirect approach to the problem. Since any infection incites antibody production, standard immunological methods ought to reveal it. Reveal it they do, but the amount of antibody detected, it turns out, fails to correlate with the seriousness of symptoms, or the density of microfilariae in the blood. More damning yet, as Robert Hamilton noted in one review of the subject, the antibody strategy makes for "an unreliable method for discriminating between past and present infection." That is, finding antibodies doesn't tell you whether the infection they arose to combat is new or was cured long ago.

The newer approach to diagnosing filariasis is to look for direct evidence of infection. If there are microfilariae or adult worms in the body then they ought to betray signs of their existence. In effect, as Eric Ottesen pictures it, these living organisms urinate and defecate, and the products of those bodily processes ought to be detectable. So, the new strategy goes, look not for evidence of immune response to the worms, but rather for evidence of the worms themselves—more particularly those parts of the worms that may provoke an immune response. In short, search not for antibodies, but for antigens.

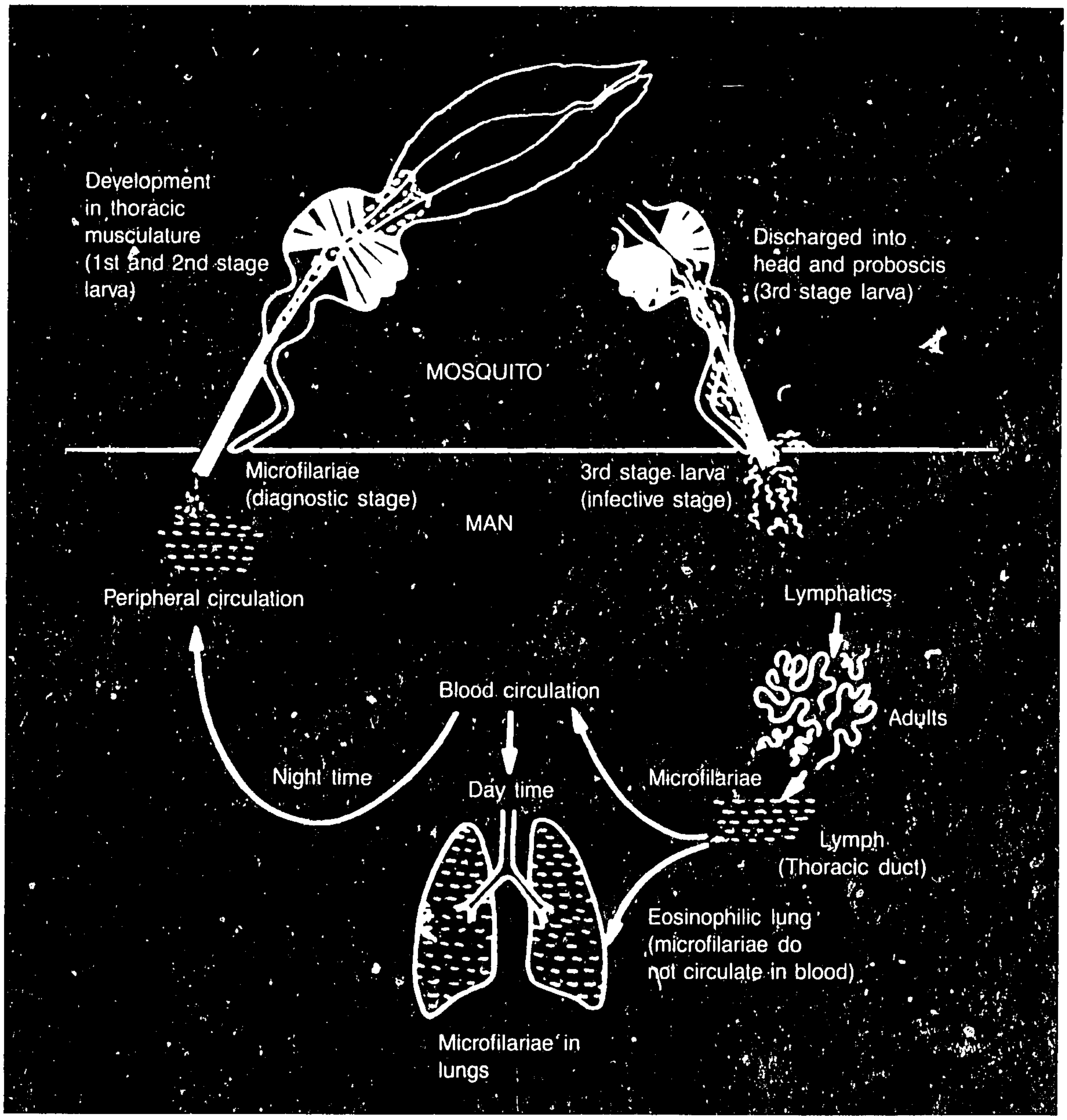
An open sewer in south India breeds mosquitos that can carry larvae of the parasitic worm Wuchereria bancrofti, *which infect humans, causing the grotesque swelling known as filariasis.*

In filariasis, diagnosis is the real sticking point. A blood sample of an infected person may appear barren of baby worms at noon, while at midnight it contains concentrations of 10,000 per milliliter.

One successful shot at the problem was taken by Hamilton, then still at Johns Hopkins University, Ottesen, and a colleague, Rabia Hussain, using a technique known as immunoradiometric assay, or IRMA. The test relied on radioactively labeled reagents, making it ill-suited for the rigors of the field. But then, under STI, the same three researchers plus Ottesen's NIAID colleague Thomas Nutman and Indian collaborator Ramesh S. Paranjape of the Tuberculosis Research Center, went on to learn something about the antigen their IRMA had detected. It was probably a glycoprotein, had a molecular weight of about 210,000, was resistant to acid and to boiling, and so on. With further work, they reasoned, it should be possible to raise monoclonal antibodies to the antigen, which could then be used to extract it from blood samples. They'd then have the makings of a diagnostic marker for filariasis better suited to field screening.

Already moving his filariasis diagnosing methods out from the laboratory and into the field is Gary Weil, based at Washington University Medical Center in St. Louis. Weil had earlier used a technique called counterimmunoelectrophoresis for detecting a worm, *Dirofilaria immitis*, that infects the hearts of dogs, causing death by heart failure. "The success of this approach," he concluded in a paper detailing it, "invites parallel studies with the important filarial parasites of humans." Under STI, Weil accepted his own invitation, successfully applying it to human filariasis, then following up with an even more sensitive method called enzyme-linked immunosorbent assay, or ELISA.

In ELISA, you first pull the desired antigen from the blood sample with a monoclonal antibody specific for it. Then you add more monoclonal antibody, this time linked to an enzyme—a substance which, acting on a "substrate," speeds its



Like other parasites, **Wuchereria bancrofti** *has a complex life cycle involving infestation of both insects and man. In the mosquito, the larvae develop through three stages, the third of which infects man. When a mosquito bites a human, larvae lodge in lymph nodes in the groin and elsewhere, growing to lengths of three or four inches. As larvae clog the lymphatics, legs, scrota, and breasts swell to immense size. The larvae grow to adult worms, mate, and produce thousands of microscopic worms, some of which lodge in the lungs to produce a variant of filariasis known as tropical pulmonary eosinophilia causing shortness of breath. Other microfilariae live in the blood stream, reaching their maximum concentrations at night; these microfilariae can be ingested by mosquitos, starting the cycle all over again.*

biochemical transformation into something else. Of course, it's not just any enzyme you use, but one the end product of whose activity is a colored stain. Add the substrate, measure the intensity of the stain with a special reader and, leaving aside methodological twists, you know how much antigen there is to which the enzyme-linked antibody has stuck. The darker the stain, the more antigen in the original sample. Weil's ELISA worked. Tested on subjects in the southern Indian state of Kerala, it reliably tested negative on all 35 uninfected controls, positive on all 27 patients whose night bloods showed microfilariae, and was not fooled by parasites from other organisms.

There was only one hitch. Much more blood was needed than in the traditional night bloods, which require only enough to smear a glass slide. And for a mass screening, that wouldn't do at all. Most Indians, explains S. Santhanam, one of Weil's collaborators at the National Institute of Communicable Diseases in Delhi, are not as accustomed to giving blood as are Westerners. American researchers tell of villagers superstitious about giving blood samples, fearful that it might undermine their manhood, or even suspicious that the blood might be sold for profit.

Then, too, Santhanam points out, when it comes to mass screening, numbers count. Which means that time counts. And sitting the patient down, calming his jitters, preparing needle and syringe, baring the vein, drawing the blood, and transferring it to a tube can take five or ten minutes. That they had been able to get enough villagers for their research was testimony, says Santhanam, to the "confidence built up over the years" by NICD's field work. But that wouldn't apply elsewhere, in a mass screening. On a large scale, Santhanam declares flatly, "You can't take venous blood from the population." Something quicker, simpler, and less invasive was required:

Like a fingerprick test, in which a few drops of blood from a pricked fingertip are allowed to seep onto a piece of filter paper. Refining their early ELISA to gain the needed sensitivity and comparing it to the original on eighty-five subjects, they found they'd lost only the most marginal filaremics. Missing "one or two per cent," Santhanam points out, is a small price to pay for testing 50,000 people in the time otherwise spent testing 5,000.

At the filariasis clinic in Calicut, an Indian woman exhibits her grotesquely enlarged leg, typical of the disease.

As part of STI, Santhanam and another Indian STI researcher, D. C. Jain, spent eight weeks in the United States during the late spring of 1985. After arriving at Kennedy Airport in New York, they were off to St. Louis, where Weil picked them up, gave them a tour of the city, showed them the Gateway Arch, ensconced them in a hotel near campus, and soon had them at work in the lab. For a week, Santhanam did cell cloning and other aspects of monoclonal technology in the Washington University hybridoma facility, which turns out monoclonal antibodies for 50 or more labs in the research complex.

For Santhanam, a virologist, it was a revelation. Back in India, the ELISA technique that was the basis of Weil's field test was no longer new, and monoclonal antibodies were being used routinely. But this hybridoma center—that was a marvel, and when she got back to India she was lauding its virtues to her colleagues, lobbying for the Indian Council for Medical Research, the country's NIH, to set up something like it. Why, it wouldn't much matter which ICMR institute got it; all would profit from it. "If it comes," she sighs, "it will be very good."

After her four weeks in St. Louis, punctuated by a three-day trip with Weil and Jain to the Center for Disease Control in Atlanta, Santhanam traveled to Ann Arbor for a month with Eugene Higashi of the University of Michigan. With Higashi, whose

All six women are outwardly healthy, but three of them carry thousands of microscopic worms, which can be ingested by mosquitos to infect others. STI researchers are searching for a rapid and effective diagnosis of filariasis, the first step toward a vaccine.

experience with filariasis goes back to the 1960s when he was stationed at a Johns Hopkins field station in Calcutta, the work was very different. Higashi wasn't tackling the diagnosis problem. Rather, he wanted to know just what provoked the strong immune response that caused the lymphatic blockage. Higashi was grappling with a fundamental question, one on which, as Santhanam says, "everyone is still groping in the dark."

Higashi's strategy was nothing if not straightforward. Collect a 20 milliliter sample of blood from each patient, extract the lymphocytes from each, culture them, incubate them for a week, then stimulate the cultures, one by one, with a variety of antigens—ground up adult worms, ground up larvae, microfilariae, anything they could think of. Feed the cultures radioactive thymidine, known to be taken up during cell division. The resulting radioactivity levels would then be a measure of lymphocyte proliferation—the higher the counts, the "hotter" the cultures, the more they'd immunologically responded to the antigen.

They collected blood from three groups of patients, all from an endemic area in southern India around NICD's Rajahmundry Regional Filaria Training and Research Center. First were classic, elephantiasis-ridden victims. Second, those whose blood bore microfilariae but who showed no symptoms—carriers who, outwardly healthy, serve as a microfilaremic reservoir for the mosquitos that transmit the disease. Third were "endemic normals," who lived in the region and had presumably been bitten by *W. bancrofti*-bearing mosquitos all their lives, yet showed no evidence of infection.

It was this last group, the endemic normals, who were the key. "Maybe we can identify something unusual in them that would give us a clue toward a vaccine," says Higashi. In other words, they must be doing something right, and Higashi wanted to learn what it was. (In fact, Higashi points out, the endemic normals are not a homogenous group at all. Most show a strong antibody response that suggests having once beaten back the disease; the minority who do not may have just been lucky up to now, making them sitting ducks for the disease in the future.)

"So far, we have not come up with anything spectacular," says Higashi; their review of the data was still incomplete, but as yet they'd spotted no clear differences among the three groups. Perhaps, he speculated, the next step was to break down the crude antigen soups they'd been using into individual proteins, then see what effects they had on the cultures. Maybe that would

An authority on diseases, some of which affect only a few thousand people worldwide, he found himself in Madras face to face with a disease that afflicted millions.

get them closer to the "something right" the endemic normals were doing.

At the Tuberculosis Research Center in Madras, at least one STI project has borne results that, while not exactly "spectacular," are at least satisfyingly certain and concrete: three weeks of DEC are not enough.

At TRC, a prime target of the collaborative research has been a rare variant of "big leg" filariasis known as tropical pulmonary eosinophilia. Sometimes misdiagnosed as tuberculosis, TPE is thought to be caused by an over-strong immune response to the filarial parasite. The blood contains no microfilariae; the immune response has destroyed them. But, according to one theory, microfilariae trapped in the lungs break down, causing local inflammation. In any case, victims are left short of breath; they cough, wheeze, lose weight. Under the stethoscope, reports STI scientist Ronald G. Crystal of the National Heart, Lung, and Blood Institute, their lungs make a "dry crackling sound, like Velcro."

Before STI, Crystal had never encountered a case of filariasis, his knowledge of the disease being confined to textbooks. But he was a world expert in lower respiratory tract diseases and a pioneer in the technique known as bronchoalveolar lavage. Lavage, says Crystal, is essentially "a liquid biopsy." With a long, snakelike fiberoptic bronchoscope, you squirt saline solution directly into the lungs, "washing" them, then suck back up cells from the lungs and the fluids bathing them, and study them. The technique had already been applied to some 2,000 pulmonary patients at NIH. And Eric Ottesen, talent scout for STI's filariasis program, could see it profitably applied to tropical pulmonary eosinophilia; maybe they could finally learn what was going on in the lungs of these patients. He approached Crystal, and Crystal signed on. On an initial trip to Madras, Crystal reconnoitered the territory, as it were, "meeting the players, seeing the patients." First impression? Setting up a lavage suite at TRC, half a world away from NIH's high-tech embrace, "would be like doing it on the moon." Still, he became convinced they could do it, and soon he and his coworkers were moving an entire lavage facility to Madras. Maybe two tons of equipment in all, Crystal guesses.

The equipment was set up in a bare, fluorescent-lit room, once a doctors' office, more recently a conference room, ventilated by an overhead ceiling fan. Soon, Indian physicians under V. K. Vijayan had absorbed what they needed from Crystal and his technicians and were performing lavages themselves. Patients began coming through, more than a hundred so far. Data piled up.

Noted from the first was that the long accepted treatment for tropical pulmonary eosinophilia—three weeks of DEC, six milligrams per kilogram of body weight per day—was not sufficient. Yes, there was marked clinical improvement. But no, lung inflammation was not irrevocably halted. Some patients developed, months later, a chronic form of TPE that often led to pulmonary fibrosis. Perhaps, Crystal and his collaborators began to think, more than three weeks of DEC were needed. Or maybe, as early tests hinted, corticosteroid treatment would reduce the inflammation. Future studies would tell.

Compared with his work back at NIH, starting up a lavage suite in Madras was a scientifically modest undertaking, but Crystal found it a deeply satisfying one. An authority on diseases some of which affect only a few thousand people worldwide, he found himself, midst the crippling pathology he saw in Madras, face to face with a disease that afflicted millions. "It was," he says, "quite humbling."

And quite exhilarating to have a hand in doing something about it.

Robert Kanigel is a freelance writer living in Baltimore, Maryland.

At the Aravind Eye Hospital in Madurai, Dr. Natchiar, senior medical officer and sister of the hospital's founder, tests a young boy on whom she recently operated for congenital cataract disease by asking him to show her how many fingers she is holding up. The boy's correct response demonstrates the operation was a success.

Second Sight

Preventing and curing blindness in the young, the middle-aged, and the old.

by Judith Randal

Fifty-eight is mandatory retirement age for Indian civil servants. But when 58 came for Govindappa Venkataswamy, in 1976, the chief of ophthalmology at the government hospital in Madurai, the physician and surgeon had other plans. Despite a long history of painful rheumatoid arthritis in his hands, he not only decided to continue operating as long as he did not endanger patients, but to tackle a problem that had frustrated him for his entire career: the sheer inability of the government health service to begin to meet the needs of millions of Indians with visual disorders, a large proportion of them blind. The result is Madurai's Aravind Eye Hospital, an enterprise that consumes the total energies of both Venkataswamy himself and his extended family—four of them ophthalmologists, one a hospital administrator who honed his professional skills at the University of Michigan's School of Hospital Administration, and one who sees to it that the optical shop on the premises, a commercial venture, accurately fills eyeglass prescriptions in timely fashion and does not overcharge.

From a modest 20-bed beginning in a house that now serves as a hotel (managed by another member of the Venkataswamy clan) for ophthalmic residents from both India and the United States and for a variety of other visiting health professional volunteers, the hospital has grown into a 600-bed institution built by still another member of the family, one of Venkataswamy's brothers who is an architect and contractor. With its own school for ophthalmic nursing, dispensing pharmacy, X-ray department, microbiology laboratory, and outlying clinics, the hospital is accredited by the World Health Organization and the Medical Council of India and has the most modern equipment, including lasers and an ultrasound scanner, and computer facilities for research as well as bookkeeping.

Meanwhile, a second and younger generation of Venkataswamy relatives is in medical school also preparing to specialize in ophthalmology. The hospital already has satellite units elsewhere in Tamil Nadu, the part of southern India where Madurai is located, and in the neighboring state of Kerala and regularly sends staff units to Nepal to help in the fight against blindness there. Venkataswamy envisions still more satellites elsewhere. Although opthalmologists who are not related to him are already a welcome part of the Aravind endeavor, Venkataswamy, himself a bachelor, wants to be sure the tradition of service he has started does not die with him and continues to grow.

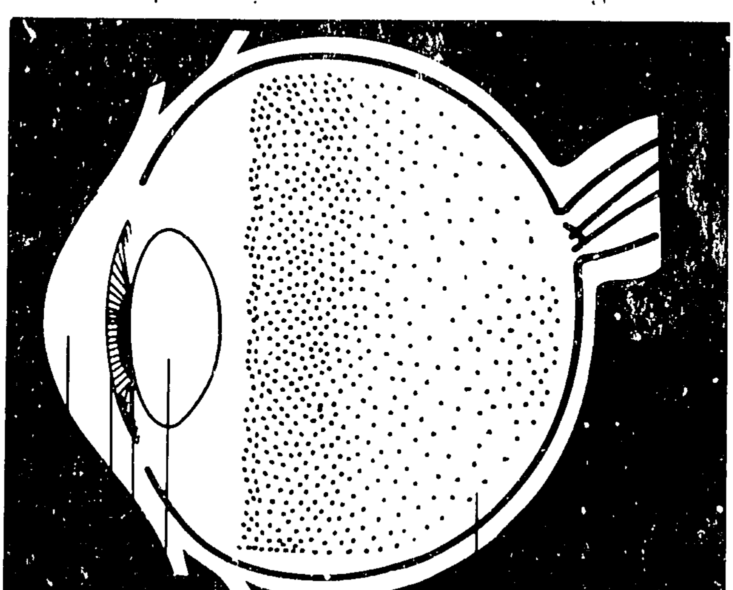
Aravind is, in microcosm, what the Indo-United States Science and Technology Initiative (STI) is all about. It is relevant to the overall STI for three reasons: First, research on blindness is a major component of the STI program, because blindness is an important human affliction in both India and the United States. Second, the hospital itself is a participant in one important STI research project area. And third, Aravind's patients are typical of those with eye disorders throughout India, and their afflictions are similar to some American visual disabilities.

Venkataswamy's enterprise meets its costs primarily through the fees charged to paying patients. And they are not exorbitant.

Holding onto each other for guidance, these blind men wait in line for cataract surgery at one of 40 surgical eye camps the Aravind Eye Hospital runs in Tamil Nadu state in southern India.

Cataract surgery costs $40 to $50 per eye; with the implantation of intraocular lenses, the price rises to about $150 per eye. Either way, patients are usually hospitalized for five days at $3.00 a day. In 1985, the hospital performed 24,780 operations, of which 17,586 were performed without charge. Moreover, Aravind does not wait for the indigent blind to show up on its doorstep. Virtually every day of the year it sends teams into the rural villages of southern India by van to seek out people who need its help.

So-called eye camps of this type, primarily for the detection and surgical treatment of cataract, are commonplace in India. Many of them, however, have been criticized because of inadequate follow-up care in general and failure to provide cataract spectacles in particular. A cataract is a disease in which the lens has become so clouded that it no longer admits sufficient light. Surgical removal of the opaque lens corrects that problem, but loss of the lens deprives the eye of its focusing power, so it no longer perceives images. Without spectacles that restore this ability to focus, eyes operated on for cataract are still functionally blind.



The eye consists of the cornea, a transparent window protecting the pupil, the hole that admits light. The colored iris is controlled by muscles that open and close the pupil, adjusting it to differing light levels. The lens focuses the light on the retina, the collection of light-sensitive cells at the back of the eye that send messages via the optic nerve to the brain.

Aravind eye camps, of which 496 were conducted in 1985 alone, do not leave their cataract patients in this kind of a lurch. Instead, it is the hospital's policy to transport patients to its main Madurai facility for surgery or to a 60-bed satellite facility in Theni, Kerala, which opened last year. Patients are operated on in up-to-date surgical suites, convalesce under medical supervision for six days, and get cataract lenses before discharge. Some, primarily younger patients whose occupations demand keen sight, are fitted with intraocular lenses, just as are their more affluent counterparts. Free transportion to and from their villages are part and parcel of the package. And at the Madurai facility, there is hot water for bathing, a luxury most poor Indians otherwise do not have an opportunity to enjoy.

Not content with what his institution is already doing, Venkataswamy has embarked on what he calls social marketing. Despite the hospital's efforts, many of the cataract blind in Tamil Nadu, particularly those living in rural areas, fail to avail themselves of care. In collaboration with the United States National Institute of Health's National Eye Institute, and the University of Michigan, the hospital has identified the barriers responsible and soon will begin to test strategies to correct the problem. At the same time, work under this aspect of STI also is going on in two of India's most important cities: New Delhi, the capital, and Hyderabad in the south central section of the sub-continent.

In New Delhi at the Rajendra Prasad Center for Ophthalmic Sciences of the All India Institute of Medical Sciences, Madan Mohan and his colleagues are, as part of the STI initiative, studying risk factors for cataract. Cataracts are a major health problem in both the United States and India but for somewhat different reasons. In the United States they develop after age 65, whereas in India, they tend to occur between the ages of 40 and 60 and are less likely to be treated. Thus despite one million cataract removals a year in India, there is a backlog of six million untreated cases that continues to grow. As life expectancy lengthens there, the situation is bound to get worse. The United States has no such backlog, but its

Aravind does not wait for the indigent blind to show up on its doorstep. Virtually every day of the year it sends teams into rural villages to seek them out.

population is also aging. While surgery and corrective lenses restore useful vision to the vast majority of Americans with cataracts, the operations occasionally fail. Furthermore, therapy does not come cheap. Cataract surgery alone is costing the nation $1.4 billion annually, most of it largely paid for by Medicare.

If the onset of cataracts could be postponed by a decade, both nations would benefit. In India, this would mean 45 per cent fewer people in need of treatment. And in the United States, it would reduce the number of cataract operations by almost half, saving as much as $600 million a year.

Since cataracts are not an inevitable aspect of aging, the objective of Mohan's study is to try to identify risk factors for this disorder by comparing people in the same age range—in this case 40 to 60—who have cataracts with those who do not. Assuming such risk factors can be detected, it may eventually be possible to modify them by designing interventions that would protect the lens of the eye.

Cataracts vary biochemically and in other respects according to where they are located: in the center of the lens or nucleus, in the lens's periphery or cortex, or in a portion of the capsule surrounding the entire lens. Some cataracts, in fact, affect more than one region of the lens. So Mohan wants to determine whether, as he suspects, there is a correlation between specific risk factors and the type of cataract that results. To test this hypothesis, he and his colleagues have carefully recruited representative numbers of patients with each type of cataract, about 1,140 patients in all. The researchers have taken careful case histories of them along with 400 controls, who have no cataracts, to catalogue their exposures to smoke, sunlight and dust, smoking habits (if any), health records, economic and educational status, and a variety of other variables.

Dr. Natchiar and a clinician adjust the bandages on a cataract patient after making sure that his eye is healing properly.

After cataract surgery, a clinican checks to see that patients are resting comfortably and their bandages are properly in place. At Aravind, eye surgeons perform 100 operations a day on average.

There is evidence to suggest, for example, that short stature or low weight to height ratio reflect a greater risk of cataracts, as do high blood pressure and having worn glasses for nearsightedness. The Biometry and Epidemiology Program of the United States National Eye Institute is assisting in the computer analysis of this data.

The results of population studies and animal experiments suggest that vitamin and trace mineral deficiencies, as well as skimpy protein intake and abnormally low levels of certain red blood cell enzymes, may also predispose to cataracts. To further explore the possible impact of these and other nutritional factors on the health of the eye lens, researchers interviewed all participants about their past and present eating habits and took blood samples from some, which the Biometry and Epidemiology Program at the National Eye Institute is also helping to analyze. Such a complex study takes time. But according to Robert Sperduto at the National Eye Institute, a principle investigator on the project, some preliminary findings may be available by mid-1987.

But blindness is not just a disease of old people. Moving down the age scale, Eales' disease, first described by Henry Eales, a nineteenth century British ophthalmologist, blinds young men in the most productive period of their lives, between the ages of 20 and 30. Rare in the United States—the Wilmer Eye Institute at Johns Hopkins Hospital in Baltimore, for example, has seen only about 60 cases in the last 50 years—this disorder is nonetheless of interest to both countries. In India, Eales' disease blinds one to two percent of young men, while in the United States, diabetic eye disease is the leading cause of blindness in both sexes from the ages of 20 to 60. As the two disorders are similar in some respects, what is learned about one may deepen understanding of the other and so help bring both under control.

Both Eales' disease and diabetic eye disease are retinopathics: they attack the blood vessels in the retina, the collection of light-sensitive cells at the back of the eye that send messages via the optic nerve to the brain. Moreover, the two diseases also have in common their habit of causing retinal blood vessels to mysteriously multiply which, in turn, results in their leaking. The more blood spilling into the normally clear fluid in the eye, the cloudier vision becomes.

To be sure, blood vessels tend to behave somewhat differently in the two disorders with inflammation the primary feature in Eales' disease and degeneration of these vessels more prominent in the eyes of

Since Eales' disease and diabetic retinopathy are similar in some respects, what is learned about one may deepen understanding of the other and so help bring both under control.

diabetics. But as Carl Kupfer, director of the National Institutes of Health's National Eye Institute and a participant in this STI project, explains, the very fact that both disorders attack the blood vessels of the retina is a promising springboard for research. So it is that Eales' disease is being approached from two directions.

The one of most immediate potential benefit to patients is the use, at Aravind Eye Hospital, of a device called a xenon arc photocoagulator. In Eales' disease, not only do retinal blood vessels leak, but the leakage leads to scarring which ultimately causes the retina to break loose from its moorings. A xenon arc photocoagulator generates intense light, which can be used to both seal the leaky blood vessels and, in effect, "spot weld," detached retinas into place. The treatment, preceded by briefly freezing the eye with a liquid nitrogen probe to forestall hemorrhage, is still experimental, because xenon arc photocoagulation is now being used for the first time in Eales' disease.

Patients typically seek medical attention because of hemorrhage and loss of vision in

Using a flashlight a pediatric opthalmologist peers into the eyes of a small boy, the first stage of a routine eye exam.

one eye. But when doctors examine the other eye, they find that it, too, is affected. Thus, if patients agree (informed consent is an important part of the program), they are randomly assigned either to have only one eye treated or to participate in a second part of the study in which some patients are treated with xenon arc therapy and some are simply followed and observed on a regular basis. Heartless though this may seem, it would be impossible to get a true reading of the effectiveness of the treatment otherwise. Randomization eliminates bias on the part of the patients, doctors, and scientists. Only when studies are designed in this way, is it possible to determine whether, in fact, almost any previously untried therapy has any impact on the course of a disease and, if so, whether it does more good than harm. Thus randomized controlled clinical trials of this kind are the gold standard of medical research around the world.

It will take more patients than the several dozen already participating in the project to provide a definitive answer as to whether or not the treatment works and how long its possible benefits last. But with no dearth of suitable candidates for the therapy, a definitive answer is pretty much assured.

In the process, Aravind Hospital physicians expect to learn from closely following both eyes of every patient more about the behavior of this previously little-studied disease. They have already learned, for example, that although the predilection of Eales' disease for men suggests that it might, like hemophilia, be genetically determined by a defect on the X chromosome, no patient has yet turned up who has a relative with the disease.

Meanwhile, evidence suggests that there may be something about the immune system of diabetics that causes it to turn on patients' blood vessels in many organs, including those of the eye. Although Eales' disease differs from diabetes in that only retinal blood vessels are its target, the suspicion is that it, too, may represent a malfunction of the immune system: white blood cells known as T cells may undergo some sort of biochemical change that play havoc with the blood vessels of the retina. Accordingly, Eales'

Collaborators in the STI projects of the United States National Eye Institute and the Indian National Institute of Nutrition meet at the NEI to develop detailed reseaich protocols. Barbara Underwood at left and Carl Kupfer at head of the table run the American projects.

disease patients participating in the clinical studies at the Aravind Eye Hospital are asked to give blood samples for research. If they consent, and not all do, those samples are sent to the laboratory of Veerappan Muthukkaruppan, Professor of Immunology at Madurai Kamaraj University, about ten miles away.

Muthukkaruppan, 52, got his undergraduate training in India, but earned his Ph.D. in zoology and developmental biology under the tutelage of Professor Robert Auerbach at the University of Wisconsin at Madision in 1965. Muthukkaruppan has been particularly interested in the eye since his graduate student days in Madison, and he is currently one of 30 National Fellows, one of the highest honors that India confers on its academics.

Any United States scientist visiting Muthukkaruppan's laboratory would find it somewhat spartan and might be frustrated at the unreliability of the power supply, which sometimes slows the progress of experiments. Nonetheless, Muthukkaruppan and his graduate students use standard molecular biology equipment (some of it bought with Indian and United States STI funds) and their work is meticulous and painstaking.

Fundamental to the collaborative approach that Muthukkaruppan and the National Eye Institute have worked out is a comparison of Eales' disease patients' blood with that of healthy controls. Looking for differences is a long slow search. Shortly after the project started in 1984, for example, Muthukkaruppan and his graduate students treated the blood of Eales' disease patients and the blood of healthy controls with purified protein derivative (PPD), a test that determines whether there has been previous infection with tuberculosis bacilli. What they found, to their disappointment, was that there were positive and negative responders in both groups. But upon analyzing the data, they also found that among blood samples of both groups that tested positive, the strength of the reaction was at least twice as great in Eales' disease patients as in controls.

Muthukkaruppan is not prepared to say what, if anything, this means. But one possibility is that the immune systems of people destined to get Eales' disease and those destined not to initially respond in the same way to tuberculosis or other infections but ultimately develop differences in their reactions to foreign proteins. If this theory, which he is now pursuing, is correct, it could turn out that abnormal amounts of antibody may build up in the victims' bloodstreams, eventually attacking blood vessels in the retina. Researchers around the world are vigorously studying such so-called autoimmune reactions—in effect, allergies to some of the body's own tissues—to find out what role they play in rheumatoid arthritis, multiple sclerosis, and several other disorders. So, in trying to find out whether autoimmunity causes Eales' disease, the Indo-United States Science and Technology Initiative is very much in the mainstream of biomedical research.

In the course of his research, Muthukkaruppan has found out that white blood cells of patients with uveitis, an autoimmune inflammation of the jacket of tissue surrounding the eye, multiply abnormally in the presence of a protein known as the S antigen. On the hunch that the white blood cells of Eales' disease patients might respond similarly to this antigen, he challenged them with the antigen and discovered that the cells of positive PPD responders did proliferate when treated with this protein. So did cells of some of the weak PPD responders but to a lesser extent. Muthukkaruppan is the first to say that these findings are preliminary; that blood samples from many more patients and controls must be tested with the S antigen to be sure that the initial observations are correct. Still, he seems to have found a promising lead.

Also promising are several other preliminary findings. There is, for example, a technique known as isoelectric focusing which can be used to see what patterns are produced when two or more test materials are subjected to varying degrees of acidity and alkalinity. By applying this method to the serum or colorless portion of the blood from both Eales' disease patients and normal controls, it is possible to compare the two. Results suggest that there is one small area in the overall pattern of Eales' disease sera that is different from the same area in the sera of normal subjects, much as if one had two pieces of horizontally striped fabric and found them to be alike except in one place.

A man holds a malnourished child from the slums of Hyderabad. Kids with diarrhea, like this one, are admitted to the hospital, and if they have vitamin A deficiency, the leading cause of blindness in India, they get vitamin A supplements.

The leading cause of childhood blindness in India results from inadequate intake of vitamin A.

Muthukkaruppan hopes to be able to get a more precise handle on the nature of the difference by using monoclonal antibodies—probes capable of consistently seeking out and binding to specific molecules—so that the nature and behavior of these molecules can then be studied in detail. Madurai Kamaraj University's molecular biology department is gearing up to produce the requisite monoclonals and expects to have them ready within six months.

Just when all this research will pay off is unpredictable. Eales' disease is not a new disease. But what is new, thanks to STI, is that it is now being systematically studied with modern methods for the first time. A century after it was identified, Eales' disease is no longer being taken for granted as inevitable.

Blindness from vitamin A deficiency is another problem that STI is tackling. The leading cause of childhood blindness in many developing countries, India included, results from inadequate intake of vitamin A found in green and yellow vegetables and fruits egg yolks, animal livers, and fish liver oils. In the early stages of the disease, difficulty in seeing in dim light (night blindness) occurs, and spots known as Bitot's spots, form on the white of the eye. In more advanced cases, the cornea, the structure at the front of the eye covering the iris and pupil, clouds, softens and may ulcerate—a condition known as keratomalacia. In the process, the cornea becomes scarred and loses its normal transparency so that it can no longer admit sufficient light.

None of this is news to Vinodini Reddy, 52, of the National Institute of Nutrition in Hyderabad. A pediatrician who took

A field worker interviews a mother in an urban slum of Hyderabad to see if any of her children have had measles, a disease that makes kids more susceptible to vitamin A deficiency and blindness.

postgraduate training in digestive diseases and nutrition at the Children's Hospital in Boston, she and her Hyderabad colleagues are well aware from previous studies—their own and those of others—that infections commonplace in poor third world children contribute to making their eyes vulnerable to vitamin A deficiency.

In one a series of collaborative studies with researchers at the United States National Eye Institute, for example, they found that vitamin A deficiency is aggravated by measles, and that measles virus not only attacks the eye but sometimes paves the way for secondary infections to attack it as well. It is thus becoming standard practice among public health workers to give vitamin A supplements to Indian youngsters when they get measles as virtually all of them do before age five.

Thanks largely to research by Reddy and her colleagues, Indian children who are recuperating from measles now get food supplements. Many Indian parents mistakenly believe that children should not be encouraged to eat during convalescence and so tend to serve them needlessly small portions consisting of more liquid than solid foods. As this can lead to marasmus or kwashiorkor—two forms of protein-calorie malnutrtion—public health workers are making strenuous efforts to educate the public to reverse their attitudes. (Measles immunization has recently begun in India, but what with the country's sprawling cities and 576,000 villages—many of them in remote areas—it may well take years to become universal.)

Even if measles were to vanish from India tomorrow, however, a second major child health problem would remain. This is diarrhea, the major killer of youngsters under five and often a forerunner of vitamin A blindness throughout India and most of the developing world. Fortunately, oral rehydration therapy, a simple mixture of water, sugar, and salts, is dramatically reducing the death toll from diarrhea among third world children.

Children recovering from acute diarrhea, like children recuperating from measles tend to be nutritionally vulnerable. It seems logical, therefore, that Vitamin A supplements could help protect the eyesight of diarrhea patients in the same way they aid measles patients. Before enriching oral rehydation formula with vitamin A, however, researchers have to make sure it is beneficial. One of the STI projects, which Reddy conducted, made that their business. Without the the support of Barbara Underwood, who coordinates the STI project at the United States National Eye Institute, Reddy notes, the project might never have got off the ground.

Reddy and her colleagues went to a slum area near the Hyderabad airport where they identified 19 undernourished children with diarrhea and 15 others in good health, all younger than five years old. With the permission of their parents, the researchers tested the blood of all these youngsters for vitamin A levels and followed up with 100,000 international units of the vitamin. About half of the children in both groups were given their vitamin A in plain water, while the rest received it in oral rehydration solution. In both cases, the vitamin A was radioactively labelled. This was harmless to the youngsters but allowed the researchers to use laboratory methods to detect the label in the blood and byproducts of the vitamin dose.

From these laboratory studies, the researchers learned that although the children with diarrhea absorbed less of the vitamin than the healthy children, they still absorbed 70 per cent of the 100,000

Children in a metabolic ward at the National Institute of Nutrition in Hyderabad participate in a study to find out whether collagenase (an enzyme that breaks down collagen, the gelatinlike protein that gives human cells their shape) is involved in the damage that vitamin A deficiency causes to the cornea.

Diarrhea is the major killer of youngsters under five and is often a forerunner of vitamin A blindness throughout India and most of the developing world.

international units they had been given, just 10 per cent less than youngsters in good health. The researchers also found out that it made no difference whether the children took their vitamin in plain water or in oral rehydration solution. The results of the study will be published in the Bulletin of the World Health Organization.

Researchers at India's National Institute of Nutrition are also interested in collagenase, an enzyme that breaks down collagen, the gelatinlike protein that enables cells of many types - including those of the human body and bacteria - to maintain their shapes and structural integrity. Collagenase could be a key propagator of the damage that vitamin A deficiency does to the cornea. Since collagenase often shows up in tears, Reddy and her colleagues collected tears from three groups of children, aged one to six. Children in two of the groups were suffering from severe protein-calorie malnutrition, but in only one of these groups was there evidence of vitamin A deficiency damage to the eyes. The third group of children were normal with respect both to nutritional status and their eyes.

Biochemical analysis of the tears from all three groups showed the same level of collagenase activity in those who were malnourished as in those whose nutrition - as measured by physical examinations and blood tests - was normal. But when a child was both malnourished and showed evidence of vitamin A deficiency, collagenase activity was markedly increased.

Furthermore, the extent of corneal damage seemed to determine to what degree it was reversible. All 25 children in the study with any ocular signs of vitamin A deficiency were treated with vitamin supplements. In those where the corneal damage was superficial, healing ensued and left no scars. But seven of these youngsters were not so lucky; their corneas were ulcerated. Vitamin A healed their ulcers, but the healing produced scars, leaving two of them totally blind and the other five with very limited vision.

What this suggests, is that increased collagenase activity plays a role in vitamin A blindness and that the longer the eye is subjected to this activity, the greater the likelihood that vision will be destroyed. It does not, however, answer another question. Why are collagenase levels elevated in the eyes of some malnourished children and not others? The answer isn't in yet. But collagenase is produced both by bacteria that cause infection and the white blood cells that respond to it. Thus the working hypothesis is that the presence or absence of infection determines whether vitamin A deficiency will affect vision or not.

So far, the theory is holding up well. The eyes of well-nourished children contain no organisms or very few. Nor do those of malnourished children who have healthy corneas and normal vision. But in 25 malnourished children with corneal lesions, several kinds of bacteria were present in all but two. Many more children will have to be studied before firm conclusions can be drawn. But it is beginning to look very much as if it is malnutrition complicated by infections in the eye that blind young people. The STI collaboration may chart the way to saving their sight.

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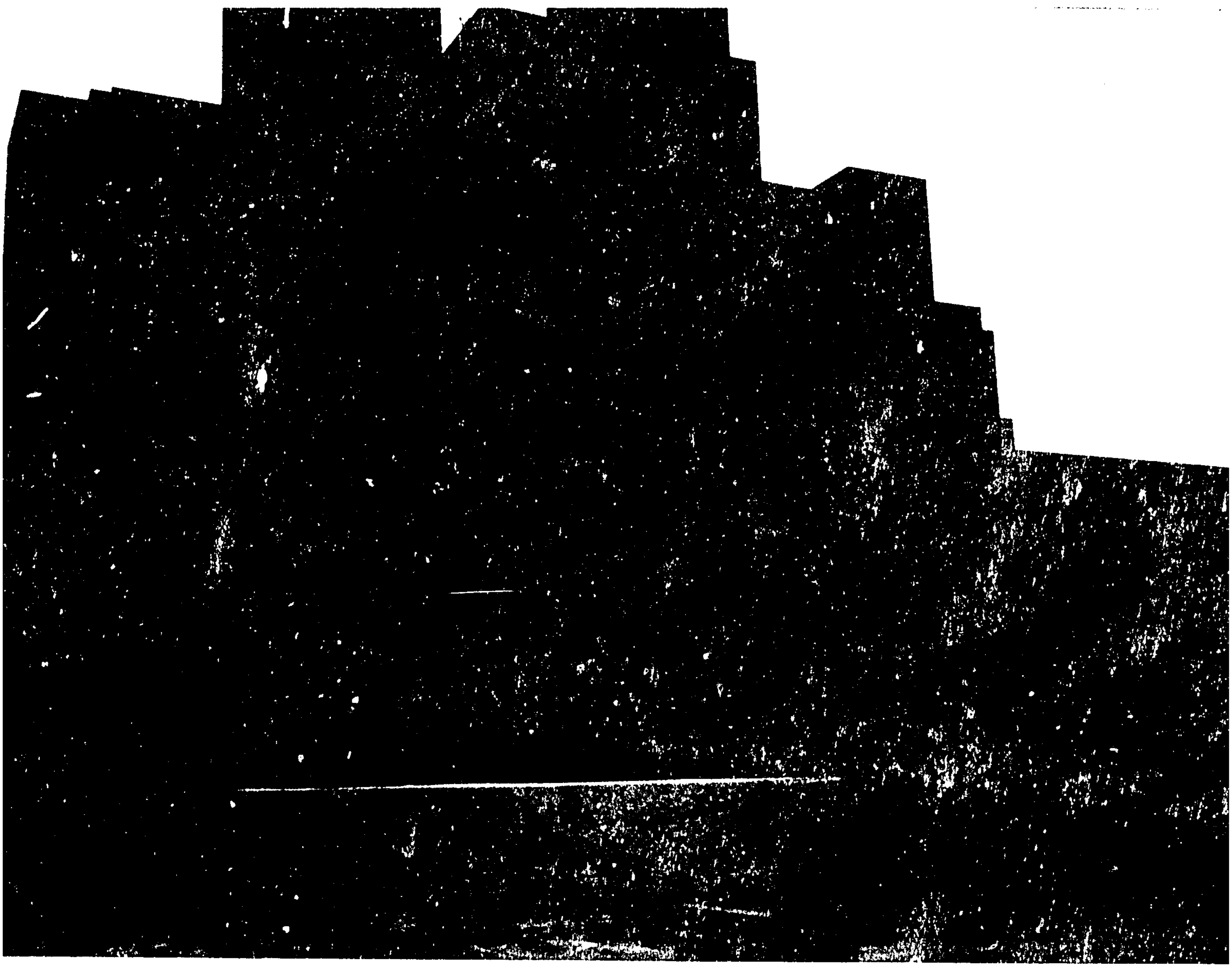


The bold and rhythmic geometic design of the brand-new National Institute of Immunology outside New Delhi is matched by the state-of-the art technology within. Here G. P. Talwar and his colleagues will employ new knowledge of the immune system to prevent conception.

Birth Control by Vaccine

Three imaginative approaches to contraception involve tricking the immune system.

by Robert Kanigel

It is dusty, raw, and unfinished atop this low hill in the southern outskirts of Delhi. Men and sari-clad women, most of them barefoot, labor in the dry, pre-monsoon heat to build India's new National Institute of Immunology. They are hurrying to finish this complex of laboratories and apartments in time for its dedication on October 2, Mahatma Gandhi's birthday. Several lab buildings are already abuzz with the whirr of centrifuges and the tinkle of laboratory glassware.

In one building the activity is quite different. As a human visitor enters their large outdoor cage, a dozen chattering baby monkeys huddle in a furry mass, then clamber away, as if a single, many-limbed organism, to the far end of the cage. These animals, each between about six months and two years old, represent the next generation of the Institute's monkey colony. But even now they furnish data; they are living proof that their parents were once fertile—key evidence, should their parents later prove infertile, for the worth of the contraceptive that presumably made them so.

A contraceptive vaccine is the prize sought by G. P. Talwar, director of the new institute, his collaborators in the United States, and other researchers in both countries working under the auspices of the Indo-United States Science and Technology Initiative. From his third floor office a few kilometers from the budding complex, Talwar supplies a sobering perspective: It took the human race until 1957 to reach the three billion population mark, but the second three billion will take only until the end of this century. Ninety percent of the increase, he points out, will come in developing countries like India. "That will impose tremendous pressures for food, clean water, shelter, education, and jobs." Talwar sees overpopulation as an epidemic not unlike the tetanus, diphtheria, or smallpox epidemics that once ravaged humankind. And it can be defeated, he declares, the same way—by a vaccine.

In Talwar's vision, shared by other STI scientists pursuing this research tack, a single injection might grant infertility for six months, a year, two years. A booster could extend that; otherwise, fertility would return naturally. With a vaccine, there'd be no remembering to take a pill. No surgery. No struggling with a condom. Pregnancy would be warded off with the same powerful immunological weapons the body uses to fight disease.

When a bacterium, say, or a virus, enters the body, the immune system raises antibodies to it. The antibodies lock onto specific parts of the foreign substance, called an antigen, neutralizing it, and setting it up for ultimate destruction.

Why not, the thinking goes, use antibodies to similarly neutralize a hormone or other protein essential to reproduction?

For sperm and egg to unite, a complex array of hormonal messengers—each, as it were, the "weakest link"—must work together flawlessly. Interrupt, shortcircuit, disrupt, or otherwise interfere with any of them and infertility can result. Doing that immunologically, through antibodies to hormones or tissue components, is the strategy common to all three STI contraceptive projects.

Bonnie Dunbar of Baylor College of Medicine in Houston visits the lab of her collaborator Shoba Sehgal in Chandigarh in January, 1986. Dunbar and Sehgal are seeking ways to make the* zona pellucida, *the thick outer coating of the egg, immune to sperm, preventing fertilization.

For Talwar, and his collaborators at the New York-based Population Council under chief C. Wayne Bardin, the targeted hormone is luteinizing hormone releasing hormone, or LHRH. A product of the brain's hypothalamus, LHRH orders the pituitary gland to secrete luteinizing hormone and follicle stimulating hormone; in males, that leads to the production of sperm.

Block LHRH and you'd sever that hormonal chain.

Block it how? By raising antibodies to it. The antibodies would mask the LHRH signal. Sperm production would grind to a halt. So would testosterone production. Maintain sexual drive through testosterone supplements and you'd have the basis for an effective male contraceptive.

Of course, getting so straightforward a concept to work is another story. Normally, the immune system is triggered by substances it identifies as foreign. But why should it deem foreign LHRH—which is, after all, produced naturally in the body? Reading it as "one of ours," the body has no reason to attack it, and normally won't.

Unless, that is, it's tricked into doing so.

The Talwar-Bardin strategy under STI has been to fool the body into responding to LHRH as if it were foreign. One approach was to make from scratch a molecular variant of LHRH that might be seen as foreign enough to marshal defenses against. Once activated, the body would raise antibodies not just to the new and different parts of the synthetic molecule but to those common to LHRH itself.

Talwar's lab synthesized a number of such LHRH variants. "It was very elegant," he says, referring to their biochemical tinkering. "It would have been the first workable synthetic vaccine." Except that none of them worked; they gave only weak or nonexistent immune response. "Once you produce the antibodies, it's molecular science," Talwar smiles ruefully. "Until then it's an art. We still don't know all the rules of the game."

So Talwar and his American collaborators, including Yun-Yen Tsong and Rosemarie Thau, who work with Bardin at the Population Council, took a safer tack. "Scientists are dreamers. But they're also realistic," says Talwar. "So we went to our old ally—tetanus toxoid."

Tetanus toxoid, a component of tetanus vaccine, is well known to provoke a strong immune response and well established as harmless to humans. What if LHRH were molecularly linked to tetanus toxoid, and this new, composite molecule used as a vaccine? The tetanus toxoid would fire up the immune system, spurring the production of antibodies to numerous sites on the composite molecule, among them the LHRH.

The collaborators found that just how and where LHRH was linked to tetanus toxoid made a big difference in the strength of the immune response. Biochemically link it at one end, and it had one effect; at the other end, or in the middle, or somewhere else, and it had quite another.

Ultimately, through one bit of immunological legerdemain or another, they succeeded in generating high enough antibody concentrations to make rats infertile, leaving a scaling up to monkeys as the next step. "The principle works," says the Population Council's Tsong. "We just have to find a good immunogen"—the ideal immune system trigger for LHRH.

Whatever an LHRH vaccine's potential as a contraceptive, Talwar notes, it may have other applications as well. Carcinoma of the prostate depends on testosterone. So does precocious puberty. Today, only castration can treat these conditions. An LHRH vaccine would achieve the same effects through what Talwar calls "immunological surgery."

Of course, as a contraceptive vaccine, this effect on testosterone production has a drawback; it makes maintenance of sex drive depend on supplementary testosterone. But what if you could interfere in the male reproductive system further along the

Chandrima Shaha of the National Institute of Immunology in New Delhi, Rosemarie Thau of the Population Council in New York, and Yun-Yen Tsong, also of the Population Council, try to develop antibodies to luteinizing hormone releasing hormone in men, a way of blocking sperm production.

But why should the immune system deem foreign LHRH—which is, after all, produced naturally in the body?

hormonal chain? Let LHRH be; let it trigger release of both luteinizing hormone and follicle stimulating hormone, or FSH. Then come in and immunologically block FSH—which stimulates sperm production, but has no effect on libido. Such a vaccine might offer the advantages of an LHRH vaccine yet avoid its shortcomings.

Among those trying to develop such a vaccine are STI collaborators N.R. Moudgal and Madhwa H.G. Raj. Once, Madhwa Raj was Moudgal's graduate student at the Indian Institute of Science in Bangalore, a middle-sized city in southern India known as a center of science and technology. Sometimes, Madhwa Raj remembers, he'd snare a monkey for an experiment by leaving a banana out on the verandah. That was back in the late 1960s. Then came a postdoc at Harvard, a faculty slot at the University of North Carolina in Chapel Hill, and finally a professorship at Louisiana State University, whose reproductive endocrinology section he now heads.

Today, through STI, Madhwa Raj once more collaborates with his old mentor, Moudgal, who directs the Center for Advanced Research in Reproductive Biology. And Moudgal's monkey colony, with some 400 animals housed in clean, well ventilated cages—no more bananas on the verandah—is one of the largest of its kind in the world devoted entirely to research.

Back in the late 1970s, Madhwa Raj and Moudgal had independently shown that neutralizing FSH immunologically could indeed inhibit sperm production in immature rats and that, as anticipated, it left testosterone production and libido alone. Those early studies were based on passive immunization; the antibodies were supplied the body artificially. Then they scaled up from rats to monkeys and from passive to active immunization—true vaccination, in which the body's immune system makes its own antibodies after being kicked on by an antigen. So far, so good.

Then came the Nieschlag bombshell.

E. Nieschlag, a West German who had earlier confirmed the Madhwa Raj and Moudgal results, in 1983 reported that in monkeys he'd kept on an anti-FSH regimen for four years, sperm counts had inexplicably climbed higher—despite still-high antibody levels. "This is something that is difficult to understand," says Gabriel Bialy, at the National Institute of Child Health and Human Development at the National Institutes of Health, manager of the American half of the contraceptive project. Were the monkeys somehow overriding the FSH antibodies? Was the whole approach flawed?

Recently, Moudgal reviewed data from some of his oldest monkeys. In the colony were four animals that had been on the FSH regimen for between seven and 13 years. All had originally been proved fertile. All had been left infertile by the FSH vaccine. All, from time to time over the years, had received booster shots. Now, he compared them to control animals of about the same age. One control, No. 309, had a sperm count per ejaculate of 140 million, about normal. The immunized No. 308 had a sperm count of virtually zero. Results for the other three old monkeys were similar. Those four oldtimers, someone told Moudgal, "are the best evidence you have.""

N.R. Moudgal at the Indian Institute of Science in Bangalore collaborates with Madhwa H.G. Raj at Louisiana State University to prevent sperm production by tricking the immune system to block follicle stimulating hormone.

Why the discrepancy between Moudgal's data and Nieschlag's? One difference, Moudgal speculates, is that Nieschlag used rhesus monkeys, while he used bonnets. Bonnet monkeys get their name from a distinctive crown of hair on their heads. But their differences from rhesus monkeys are not just cosmetic. Whereas the rhesus is fertile for six or seven months and then ceases to be fertile from about April to around the end of August, the bonnet is fertile year round. In this respect, argues Moudgal, bonnet monkeys are just like humans, making them a more appropriate model.

The FSH vaccine works. With it, sperm counts normally 200 million or so per ejaculate, drop to five or two or one million or less—low enough in the case of humans to grant de facto infertility. But is that good enough? What if messing with normal sperm production made the few sperm left abnormal? The fear is not an occasional pregnancy, but rather that any resulting fetus might turn out deformed. Accordingly, many in the field demand that any male contraceptive achieve not just low sperm production, or oligospermia, but zero sperm production, azoospermia.

Madhwa Raj, however, disagrees. Sperm in their ejaculate or not, monkeys immunized against FSH, he says, just don't seem to get normal females pregnant. Just why has been another area of collaboration with Moudgal under STI. In one visit to Moudgal's lab in July 1985, Madhwa Raj found that sperm from immunized monkeys failed to bind to the egg. Photos from that test tube study show one egg enveloped in a dense thicket of normal sperm, another almost denuded of sperm from an immunized monkey. Perhaps, Madhwa Raj wonders, the FSH vaccine doesn't just slash sperm production by a hundredfold, but also reduces the ability of those sperm that are made to recognize, bind with, or otherwise complete the fertilization of the egg? Perhaps, in Madhwa Raj's phrase, it makes them "subfertile"? He doesn't know. "I'm approaching it with an open mind," he says. "I don't know where all this will end."

The thick coat surrounding the egg through which the sperm must migrate in order to successfully fertilize it is called the zona pellucida, the target of a third STI collaboration in contraceptive vaccine development. Normally, explains STI researcher Bonnie Dunbar of Baylor College of Medicine in Houston, sperm sticks to the zona like flypaper. But if a woman had antibodies to her own zona, it might then no longer show affinity for the sperm, thereby inhibiting fertilization.

In fact, some women known to be infertile have been shown to have their own, natural antibodies to zona antigens. And some animal studies hint that development of immunity to one's own zona may be a natural part of aging. Both bits of evidence suggest the feasibility of a zona vaccine. And unlike some would-be contraceptives, which act only once fertilization takes place and can thus be construed as abortive, a zona vaccine

Young rhesus monkeys, which will play a role in the development of an anti-fertility vaccine, huddle together in G. P. Talwar's new National Institute of Immunology.

would block fertilization in the first place.

Enter the old problem: How do you trick the body into treating the zona as foreign, when it's not? Dunbar's approach has been to exploit the remarkable variety of zona pellucida among the various mammalian species. To immunize a rabbit, say, use the zona of a pig, which differs enough from that of rabbit to provoke an immune response. Some of the antibodies it raises, presumably, will be molecular segments of rabbit zona that the two species do share.

Working with a variety of colleagues over the years, Dunbar had previously shown such an approach feasible, successfully inhibiting fertility in a number of animal species. But some of that early work also showed troubling effects on normal ovarian function. And when it comes to contraceptives, side effects count heavily. "If you're dying of a disease," says Dunbar, "you're willing to accept them. But with a contraceptive, you're mostly talking about young, healthy people. You just don't have that leeway."

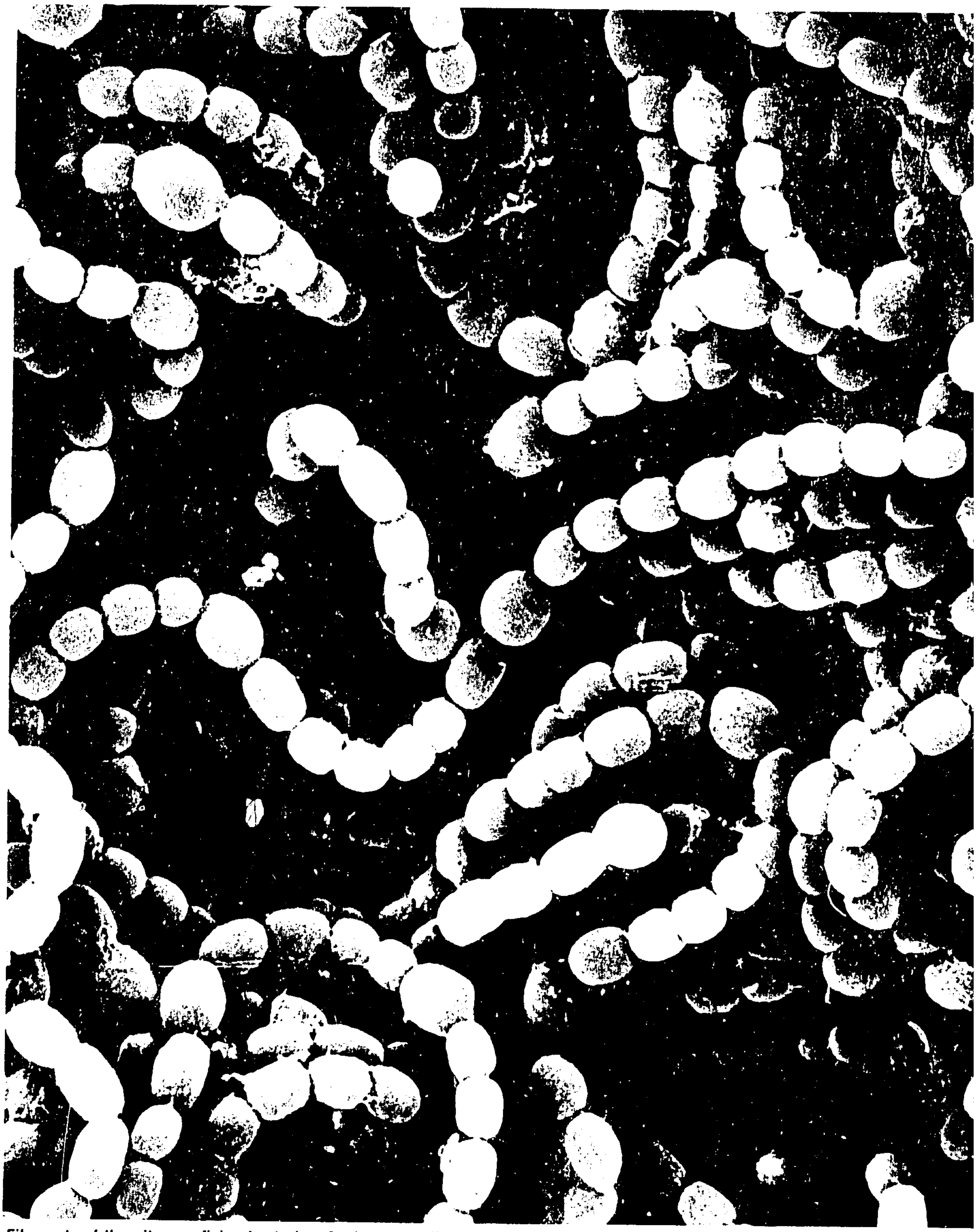
Now, under STI, Dunbar collaborates with Shoba Sehgal, a pathologist at the Post Graduate Institute in Chandigarh, to take the zona research one step further. One object of their work was to look into the ovarian side effects. Another was to transfer to Sehgal's lab some of the zona techniques Dunbar had refined over the years. A technician from Sehgal's lab visited the United States. Dunbar visited Sehgal's lab in Chandigarh, a 20-minute plane trip from Delhi. They began fertility studies both with rabbits and the monkeys maintained at Sehgal's lab. They set about purifying zona antigens, and observing the vaccine's effects on the development of ovarian follicles, in which eggs mature.

At Chandigarh—she stayed at the old British manor house on campus—Dunbar came away impressed with the monkey colonies she saw there. She heard the joke, "The students may starve here but the monkeys are fed." And it was true. "The rhesus monkeys which have been immunized with the ZP preparation," she wrote of her visit in January 1986, "were of the healthiest I have seen in captivity and the experiments have been carried out rigorously and precisely."

Much of the work was, necessarily, methodological—setting up the assays, troubleshooting problems as they came up. A problem collecting sperm from the rabbits? Try doing it, Dunbar suggested, with the animals still in their cages, on familiar ground. Certain gels, used to separate proteins, weren't gelling? Change the amount of catalyst you're using. That suggestion alone, Dunbar guesses, saved months of tedious work.

Small gains, in an ambitious project that Dunbar realizes will take years to bring off. In the early excitement over the promise of a zona-based contraceptive, she recalls, someone had predicted they'd have one within seven years. "Well," she says, "that was seven years ago. And we're still doing the basic biochemistry."

Robert Kanigel is a freelance writer living in Baltimore, Maryland.



Filaments of the nitrogen-fixing bacterium Anabaena azolla *have been isolated from the aquatic fern* Azolla mexicana *with which it lives in symbiosis. STI researchers at Battelle-Kettering are trying to understand that symbiosis well enough to improve the nitrogen-fixing ability of the bacterium, thus increasing crop yields.*

Boosting The Output of Nature's Nitrogen Factories

STI researchers augment the talent certain organisms have for converting nitrogen into fertilizer.

by Joseph Alper

"GREATEST DISCOVERY of the Century" is how the National Nitro-Culture Company's 1904 seed catalog heralded an application of biological nitrogen fixation, a process by which living organisms make ammonia from atmospheric nitrogen. The company was promoting a new bacteria-containing powder that could be added to seeds, enabling them to convert atmospheric nitrogen to ammonia to serve as the seeds' own fertilizer. This boast may seem comical today, but it foreshadowed what scientists hope they may be able to do within the coming years: harness the ability of certain microorganisms to convert nitrogen gas into usable fertilizer.

The microorganisms under scrutiny are those that contain the enzyme nitrogenase. This enzyme, formed early during evolution and found in what are considered some of the simplest microbes, is responsible for adding 90 million metric tons of nitrogen to farm fields around the world. Nitrogenase accomplishes this by breaking nitrogen gas into compounds that plants can use and producing ammonia as a byproduct.

If today's research succeeds at solving the mysteries of biological nitrogen fixation, farmers around the world might someday be able to significantly increase the yields of their crops at a small fraction of today's cost of chemical fertilizers. "We have the potential to change the way agriculture is practiced around the world if we could only understand the complex processes that make biological nitrogen fixation possible and apply that knowledge in a practical manner," says Lloyd Frederick, of United States Agency for International Development (AID).

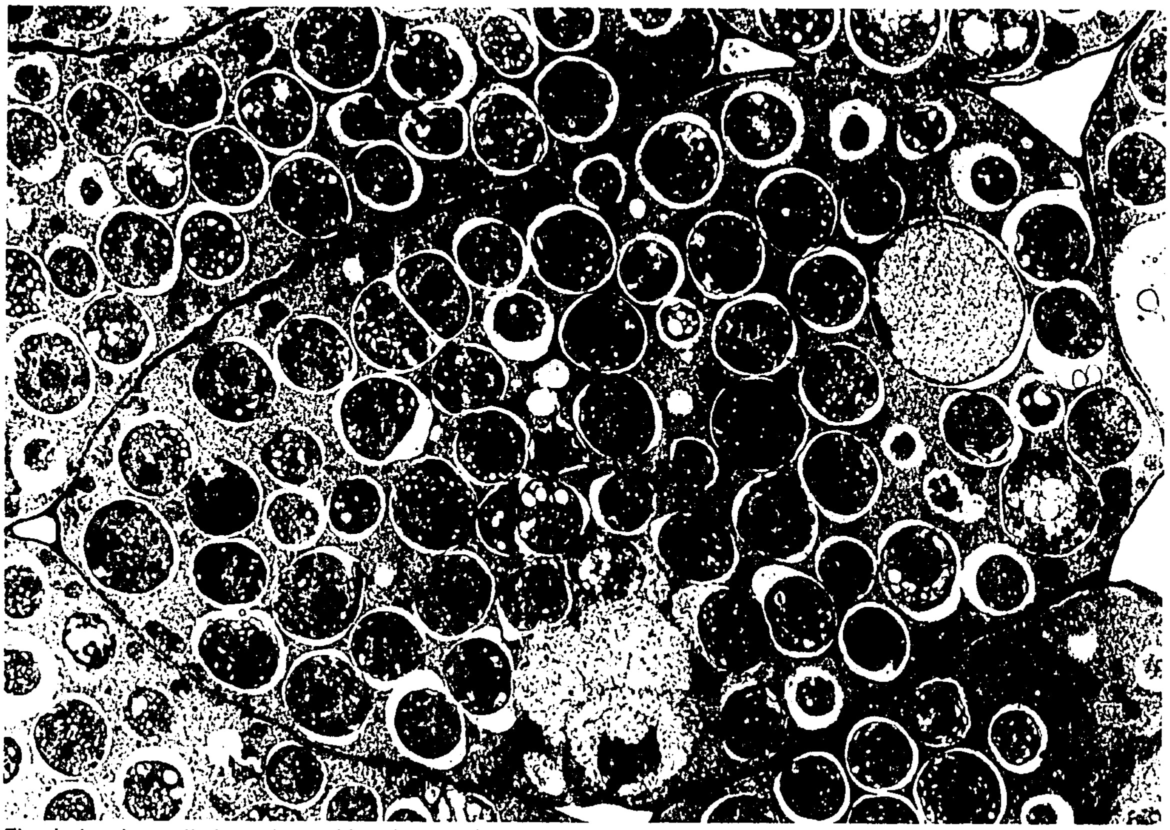
Were we able to depend on biological nitrogen fixation, a renewable resource, we could reduce the world's dependency on ever-dwindling supplies of fossil fuels needed to convert nitrogen gas to fertilizer by chemical means. In effect, a better understanding of biological nitrogen fixation would create a second green revolution, one that would benefit people in both rich and poor countries long after our supplies of oil and natural gas are exhausted.

Investigations of biological nitrogen fixation range from conventional plant breeding to state-of-the-art molecular biology. "This problem is so complex that it will take researchers working in many fields to come to grips with it," says D. W. Rains of the University of California at Davis. Some researchers, for example, are trying to learn the molecular details of how the nitrogenase enzyme converts nitrogen gas to ammonia, while others are studying the unusual symbiotic relationships that exist between some nitrogen-fixing microorganisms and certain plants.

One objective is to identify and evaluate superior strains of bacteria belonging to the *Rhizobium* genus—strains that would fix more nitrogen—and to determine the most efficient way of getting these bacteria to flourish in the soil. Another is to improve the process of nitrogen fixation by genetic manipulation. These goals have one thing in common: to get more nitrogen into the soil to feed crops growing there.

Under the biological nitrogen fixation program of the Indo-United States Science and Technology Initiative, research is focused in three areas:

- Understanding the symbiosis between leguminous plants, such as pigeon pea and



The dark spheres that dominate this micrograph are unusual photosynthetic bacteria infecting a nodule that grows on a stem of the legume* Aeschynomene. *Scientists at Battelle-Kettering were excited to find this organism as well as a nitrogen-fixing bacterium living together in symbiosis with the woody shrub.

soybean, and rhizobia bacteria. Despite decades of study, little is known about factors controlling which plant species will establish a symbiotic relationship with rhizobia. Scientists also want to learn how to improve symbiosis, which would increase the amount of nitrogen fixed.

- Deciphering the molecular genetics of nitrogen-fixing organisms. Research is aimed at uncovering the genes that are involved in nitrogen fixation, learning how they are regulated, and isolating the proteins for which the genes code.
- Comprehending the symbiosis between the aquatic fern *Azolla* and the blue-green alga *Anabaena azolla*. Among other things, this effort will involve learning more about the physical relationship between these two organisms and determining how the fern reproduces and becomes inoculated with algae. In addition, researchers want to learn more about the organisms' growth requirements and how to apply that knowledge.

Next to carbon, nitrogen is perhaps the most important element for life on earth. It is a major component of both proteins and nucleic acids—deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)—and it is used in a host of other essential compounds. But getting enough nitrogen has long been a problem for living creatures. Nitrogen deficiency, in fact, is one of the leading causes of malnutrition in the world for both plants and animals.

It is not that nitrogen is in short supply. Far from it, as we are immersed in an atmosphere that is 79 percent nitrogen. Unfortunately, that nitrogen is inaccessible to plants and animals. We must rely on the ability of certain bacteria and blue-green algae to break the bond between two nitrogen atoms, one of the strongest in nature, to make compounds that the rest of us can use.

Fortunately, the microorganisms that can fix nitrogen are ubiquitous throughout the world. Some live freely in soil or water, fixing nitrogen there. Others, such as rhizobia, live in the earth but only fix nitrogen when they form a symbiosis with a legume plant, living in nodules resembling tiny tumors on the legume's roots. Still others, such as *Anabaena azolla* can only live in a symbiotic relationship with a plant.

Regardless of their life style, these microbes are quite proficient at what they alone among all the life-forms on earth have

Regardless of their life style, these nitrogen-fixing microbes are quite proficient at what they alone among all the life-forms on earth have the ability to do.

the ability to do. Scientists estimate that bacteria and blue-green algae fix approximately 175 million metric tons of nitrogen per year, slightly more than half of that in agricultural soils. By comparison, all the chemical factories in the world make only 50 million metric tons of ammonia a year. Lightning, which converts nitrogen gas to nitrates, another usable form of nitrogen, produces only 10 million metric tons.

Utilizing the enzyme nitrogenase, microbes are able to fix nitrogen at atmospheric pressure and room temperature. To do the same thing, humans need metal catalysts developed in the early 1900s, several hundred degrees Celsius, and several hundred atmospheres of pressure.

Whether done by biological or chemical means, nitrogen's double bond is converted to ammonia by what chemists call a reduction reaction, removing oxygen by adding electrons and hydrogen ions. The reverse of reduction, oxidation, removes electrons from a molecule. For example, when enzymes in a cell oxidize glucose, they generate electrons, carbon dioxide, and water.

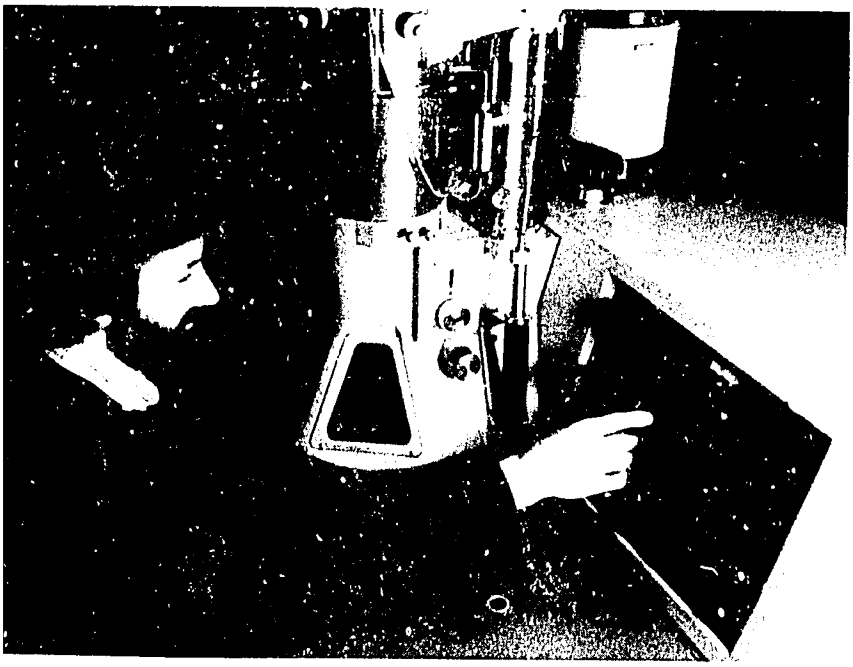
As efficient as biological nitrogen fixation may seem in comparison to the related industrial process, it is far from perfect. "We know that the nitrogenase system wastes as much as half the energy fed to it," says Peter van Berkum, an STI participant at the United States Department of Agriculture's Nitrogen Fixation and Soybean Genetics Laboratory in Beltsville, Maryland. "So one way of improving biological nitrogen fixation would be to figure out a way of suppressing this side reaction."

The nitrogenase enzyme works in concert with a number of other proteins, which form a sort of fireman's brigade, passing electrons obtained from the oxidation of molecules, such as glucose and sucrose, to the active center of the nitrogenase enzyme, where the nitrogen molecule is converted into ammonia.

As nitrogenase reduces molecular nitrogen, some protons from water are also reduced, producing hydrogen gas and wasting energy. Why this happens is still unknown. Some microorganisms, however, possess an enzyme called hydrogenase, which recycles at least some of this hydrogen, producing protons and adenosine triphosphate, or ATP, nature's primary energy source, which theoretically could be used to make more ammonia. "This hydrogen uptake system is a way in which the bacteria can recoup some of the wasted energy," says van Berkum. "But we've found that less than 25 percent of all rhizobia symbionts show this activity."

"You might think that strains possessing hydrogenase activity would be able to fix more nitrogen," van Berkum says. To find out he and visiting Indian scientist Shekhar Nautiyal tested various rhizobia strains—some with hydrogenase activity, some

With an oscilloscope Darrell E. Fleischman measures the amount of light absorbed by an* Aeschynomene *shrub to determine the efficiency with which the plant and its symbiotic bacterium convert carbon dioxide to carbohydrates. Because both bacterium and plant are photosynthetic, Battelle scientists speculate that the two together may harvest more of the light spectrum than either could do alone.



Electron microscopist Harry E. Calvert adjusts dials prior to studying* Aeschynomene*'s unique photosynthetic bacteria, which he discovered.

without—on both soybean and cowpea. The plants showed no significant difference in growth.

The experiments suggested, however, that the host plant played some role in regulating the production and recycling of hydrogen. To test this further, the two scientists screened more than 100 strains of *Rhizobium japonicum* that nodulate North American soybeans, to see if any would nodulate cowpea, a legume of commercial importance in India.

All of the strains nodulated both plants, and some were able to oxidize hydrogen when in symbiosis with either cowpea or soybean. In others, however, the hydrogen uptake system functioned only when the bacterium formed nodules on one plant species but not the other.

Van Berkum thinks that the host must produce some factor that accounts for the differences. "It might be a factor that turns the synthesis of hydrogenase on or off," he says. "In those cases where we find little or no hydrogen evolution, it may be that some hosts can influence the flow of electrons so that nitrogenase produces more ammonia than hydrogen." The latter explanation might account for the observation that hydrogenase activity does not correlate with a plant's growth rate.

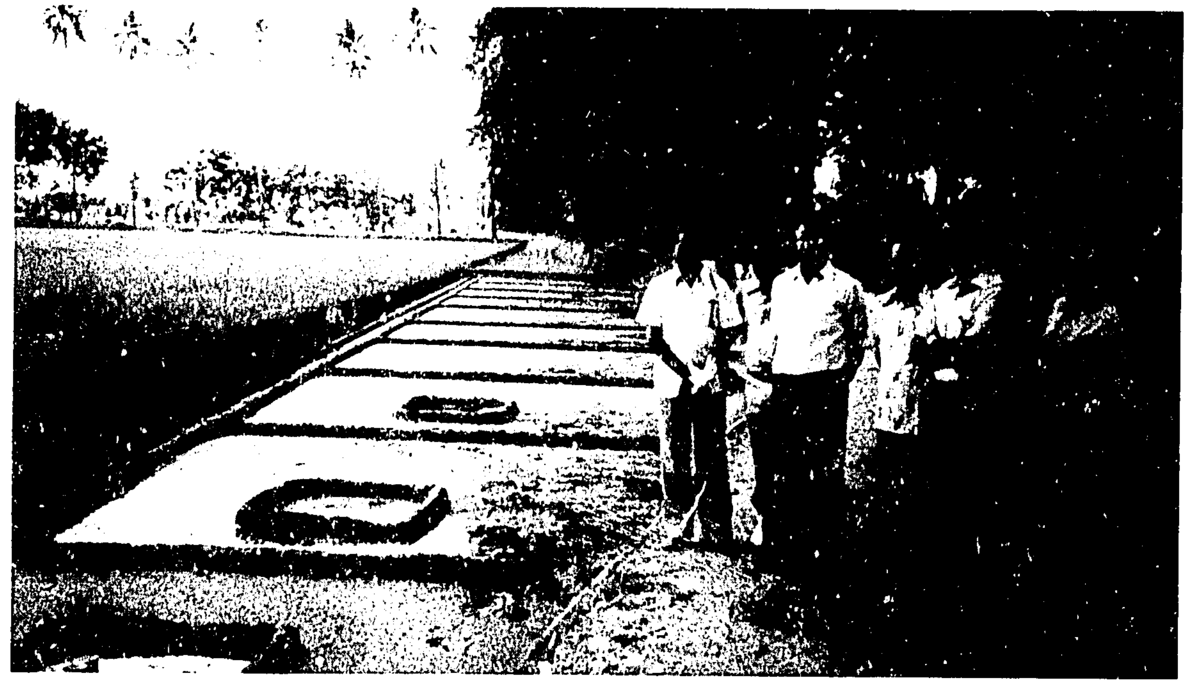
The two researchers hoped to find rhizobia strains that would nodulate pigeon pea better than those now found in Indian soils. "Both pigeon peas and soybeans are very important in India, but they nodulate very poorly in the soils there," says Nautiyal. What the researchers found were several strains of American rhizobia that were more effective in forming nodules on cultivars of Indian pigeon pea and soybean than the strain ubiquitous in Indian soil. The Indian strain, however, was able to outcompete the American ones that might prove valuable to farmers. "So if we inoculated soybean or pigeon pea seed with the better nodulating strains of rhizobia, they would not do much good because the indigenous strains would win out," Nautiyal says.

Nautiyal and van Berkum, collaborting with S. V. Hegde of the University of Agricultural Sciences in Bangalore, India, discovered, however, that pigeon pea rhizobia indigenous to India did not form nodules on American soybean cultivars. "This means we've identified a potential solution to a problem we have in India," Nautiyal says. "By breeding Indian soybean cultivars with North American cultivars that don't form nodules with Indian pigeon pea strains of rhizobia, we may be able to develop soybeans suitable for Indian soils that will only nodulate with American rhizobia, thus forming a better symbiosis with soybeans."

"Without the ability to get bacterial strains and plant cultivars from both countries, this project would have never been possible," says van Berkum. Nautiyal says, "Now we have in sight a solution to an Indian agricultural problem that can be solved by a breeding program. We couldn't have done that without cooperation between laboratories in our two countries."

Rhizobia are unique in their ability to induce nodules on the roots of leguminous plants, just as legumes are unique in their ability to house rhizobia. But wouldn't it be nice if a corn and rice could form the same type of symbiosis with these microbes. That, in fact, is one of the major goals of nitrogen fixation research. "Today, cereal crops represent the largest use of chemical fertilizers in the world," says AID's Lloyd Frederick. "That's because unlike legumes, there aren't any bacteria that will nodulate cereal plant roots. At least not yet."

The way most researchers envision accomplishing such a feat is by using genetic engineering to either introduce the required



STI researchers examine Azolla culture plots at the Rice Research Facility at Tamil Nadu University in Coimbatore, India.

legume genes into a cereal plant such as corn, or to alter the bacterial genes that control nodulation so that the bacteria will be able to infect the new plant. Either approach, however, will require a much more detailed knowledge of the nodulation process than scientists currently have.

Nodulation is a controlled, productive infection of a legume's roots via its root hairs. Whereas many free-living nitrogen-fixing microorganisms are able to meet their energy requirements through photosynthesis (using the sun's energy to make carbohydrates from carbon dixoide), rhizobia cannot. Thus, they rely on their plant host to provide carbohydrates and other sources of energy; while in return, the bacteria produce ammonia for the plant.

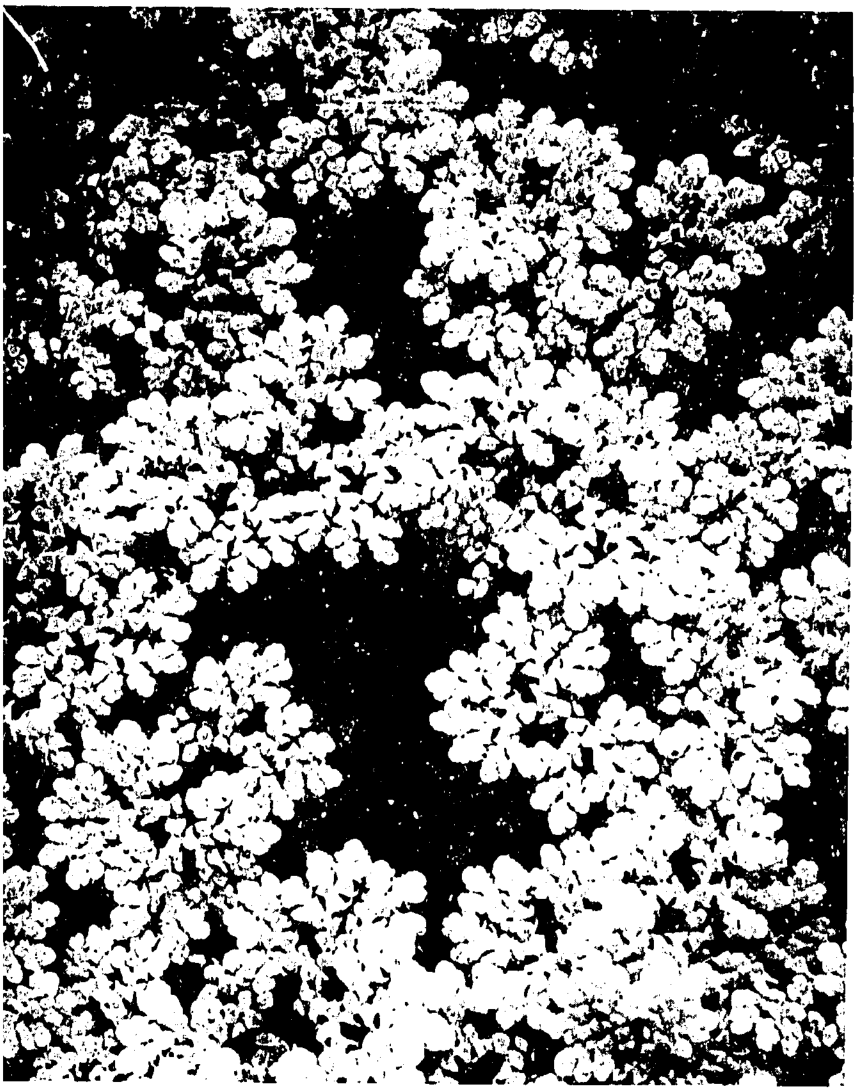
How the bacteria recognize a suitable host is not known. Some evidence suggests that there are recognition proteins on a legume's root hairs to which rhizobia can bind.

Once recognition occurs and the bacteria attach to the root hairs, they deform and produce tubes called infection threads within the cell. Harry E. Calvert, associate director of research operations at Battelle-Kettering Laboratory in Yellow Springs, Ohio, points out that rhizobia infections in soybeans occur only on growing root hairs.

Nodulation is a controlled, productive infection of a legume's roots via its root hairs.

Calvert, an electron microscopist, also discovered that many such infections occur in growing root hairs on soybean roots but that most abort before they develop into nodules. "The general idea has been that it would be good if we could increase the degree of rhizobia infection in the roots," he says. "These results suggest, however, that the infection rate is fine but that the plant possesses some means of regulating the number of nodules that will form on its roots. So perhaps we need to look for factors that determine which infections become productive nodules."

That, in fact, is one of the projects Donald Helinski at the University of California at San Diego is conducting in collaboration with scientists from the laboratories of Sushil Kumar of the Indian Agricultural Research Institute and Hiren Das of the Jawaharlal Nehru University in New Delhi. Working with fast-growing strains of rhizobia brought from India, Helinski has found gene sequences homologous to those in the infectious organism *Agrobacterium tumefaciens*, closely related to rhizobia.



At the Rice Research Facility at the University of California, Davis, Bill Rains grows two crops of Azolla *a year, providing about half his rice crop's nitrogen needs. Blue-green algae that live in symbiosis with* Azolla *provide the nitrogen.*

The agrobacter genes, called chvA and chvB (chv is short for chromosomal virulence), are essential for attachment of the bacterium to hair cells and their eventual transformation into a cancerous tumor. Using special gene manipulation techniques, Helinski and his collaborators were able to produce mutations specifically in the homologous genes in *Rhizobium melioti*, the alfalfa symbiont. "These mutants were symbiotically defective," says Helinski. "They were able to induce nodulation on alfalfa roots, but they did not infect the nodules. The interesting thing about these mutants is that the nodules looked perfectly normal, but they were empty and lacked infection threads."

Helinski has named rhizobia genes ndvA and ndvB—ndv is short for nodulation virulence—and he believes they are identical to the chv genes in the tumor producing organism, *Agrobacterium tumefaciens*. In fact, when he introduced chvA and chvB genes into the mutant rhizobia, they formed nodules that fixed nitrogen.

These mutants were symbiotically defective. They were able to induce nodulation on alfalfa roots, but they did not infect the nodules.

Joseph Thomas, of the Biology and Agriculture Division at India's Bhabha Atomic Research Center in Bombay, has found that some of the compounds on rhizobia's surface change soon after they come in contact with the root hairs of suitable host plants. Thomas inoculated cowpeas with a strain of rhizobia known to nodulate this plant. He found that within six hours after inoculation, long before any overt signs of infection or nodulation had taken place, the bacterium's capsular polysaccharides, complex sugar molecules that form a coating around the bacteria, had changed. The host-induced polysaccharides contained two new sugars, arabinose and xylose, and the relative proportions of three other sugars were different, too.

In addition, when Thomas added the host-induced compounds to roots inoculated with rhizobia, the roots were nodulated much more efficiently. None of these effects were seen, however, when the cowpeas were grown in the presence of ammonia. Thus, this phenomenon might be tied to the common observation that rhizobia do not nodulate legumes well when soils are rich in nitrogen, which is presumed to be caused by a feedback mechanism that shuts off nitrogen fixation when there is plenty of usable nitrogen in the soil.

Although researchers have found that many of the genes involved in nitrogen fixation have been conserved during evolution, this is apparently not the case with the genes involved in nodulation. Searching the genome of the slow-growing species *Rhizobium japonicum*, the primary symbiont of soybeans in the United States, Helinski was unable to find any gene sequences

Near Hyderabad in southern India agricultural researchers selectively harvest peanuts previously inoculated with different strains of rhizobia to determine how well the peanuts have nodulated and how active the nodules are. Scientists are attempting to improve the nitrogen-fixing efficiency of rhizobia bacteria in peanuts and other legumes. A more distant goal is to confer nitrogen-fixing abilities on other crops besides legumes.

homologous with the genes of fast growing species such as *Rhizobium melioti*. "Maybe the fast-growing species have a different means of inducing nodulation than the slow-growers, one that enables them to form nodules faster or more efficiently," says Helinski. "Understanding any such differences would certainly provide valuable information."

Fred Ausubel, professor of genetics at Harvard Medical School in Boston and Kate Wilson there have been collaborating with several Indian laboratories. They are searching for factors that might explain the species specificity seen in slow-growing rhizobia/legume symbioses. They were able to identify several mutations that alter a rhizobia's host range, that is, change the specificity of the plant host to fix nitrogen symbiotically.

When Wilson took several of these mutants to India for trials, she found that they actually stunted plants grown from seed inoculated with them. "They seem to have outcompeted the indigenous strains," says Ausubel. "The odd thing is that in the field trials these bacteria nodulated perfectly well, but they wouldn't fix nitrogen in the nodulated plants." It was not clear, however, whether or not the nodules contained any bacteria.

Ausubel and his coworkers were able to isolate some of the *Rhizobium melioti* genes involved in nodulation of alfalfa and transfer them to *Escherichia coli*, a bacterium that does not fix nitrogen or infect plants. With the new genes in place in the *E. coli* chromosome, the bacterium was able to produce what looked like nodules on alfalfa root hairs. These nodules were devoid of any sign of infection, however. "This suggests that relatively few rhizobia genes are involved in the earliest stages of nodulation," says Ausubel. Furthermore, these results strengthen the idea that nodulation and infection are regulated by two distinct processes.

Not all STI research is aimed at improving the nitrogen-fixation process in crop plants. A major effort involves the

STI researcher Kate Wilson, now at Harvard, grows peanuts inoculated with different strains of rhizobia in a controlled greenhouse environment near Hyderabad. Wilson is trying to identify the genes that control the bacteria's ability to recognize suitable host plants. An ultimate prospect might involve altering the genes so that different plants become hosts.

Azolla-Anabaena azollae symbiosis. For centuries, rice farmers in Southeast Asia have used the aquatic fern, *Azolla* and its symbiont, the blue-green alga, *Anabaena* as green manure to add nitrogen to rice paddies. More recently, China has implemented an aggressive *Azolla* program and credits it with producing dramatic increases in rice yields.

Azolla is found throughout the tropics and in warmer temperate zone regions. In extensive field trials, Bill Rains at Davis has found that growing two crops of *Azolla*—one as a winter green manure crop, the other as a co-crop between rows of rice—provides as much as 90 kilograms of nitrogen per hectare. That is about half of a large rice crop's nitrogen needs. In addition, *Azolla* suppressed the growth of a number of troublesome weeds that can compete with rice for nutrients.

There are several drawbacks, however, that need to be overcome before *Azolla* cultivation can become practical. For example, *Azolla* requires a large amount of phosphate to produce the maximum amount of nitrogen; it would make little sense to grow a crop that would solve one fertilizer problem while causing another. Rains has found, however, that there are several strains of the fern that require one-third as much phosphate as more common strains. Further strain selection may reduce phosphate requirements still further.

While searching for better strains of *Azolla*, Rains discovered that one indigenous to the United States, *Azolla mexicana*, actually secretes ammonia into the waters in which it grows. It appears that when *Azolla mexicana* covers the surface of the water, it starts losing ammonia. "We think that when the fern can't fix enough carbon to match the amount of nitrogen its fixing, it just dumps the excess into the water," says Rains. "It's like having a little ammonia factory right there in the rice fields."

In collaboration with S.K. Goyal of the Indian Agricultural Research Institute and S. Kannaiyan of Tamil Nadu Agricultural University in Coimbatore, Rains has now conducted field trials of *Azolla mexicana* and found that it can increase rice yields by as much as 60 percent as when conventional *Azolla* strains are used as an intercrop. The trials also revealed that *Azolla mexicana* has the heat tolerance necessary to grow well in India.

The only problem with using *Azolla* on rice fields is that you have to continually grow the plants first and then spread them over the rice paddies by hand—there is no such thing as a commercially produced *Azolla* seed. In the United States, this makes *Azolla* uneconomical. In India, the problem is that maintaining *Azolla* during the off-season takes up land that could be used to grow rice.

Most researchers believe the solution to this problem lies in controlling the fern's ability to form spores; currently, spores form under still-mysterious conditions. "If we could get *Azolla* to form spores under controlled conditions, we could then use them as seeds," says Rains. Billions of seeds could be produced in greenhouses or on small fields, which would require much less land than growing entire plants.

In addition, Rains says that being able to control sporulation, "would also make it

An Indian researcher prepares the ground for a crop of peanuts.

Rains discovered one Azolla strain that secretes ammonia into the waters in which it grows. "It's like having a little ammonia factory right there in the rice fields," he says.

easier for us to make hybrids of *Azolla*, which could lead to further improvements in the fern's usefulness.

Like all ferns, *Azolla* propagates mainly by shedding fronds—the fern's equivalent of leaves—which sprout new roots and develop into mature plants. Under some conditions, however, ferns produce sexual spores—which make egg cells and sperm. It is the goal of several STI participants to learn more about sporulation so they can use it to aid farmers.

At the Central Rice Research Institute in Cuttack, India, researchers have found that by manipulating the amount of phosphate and nitrogen in the fern's environment it is possible to enhance the amount of spores produced. Adding one ton of cow manure to *Azolla* plots increased the number of spores significantly, although the number dropped when the amount of fertilizer was increased to two tons per hectare.

At Battelle-Kettering in the United States, Gerald A. Peters, who heads the *Azolla* research program there, and Harry Calvert have been sorting out the life-cycle of *Azolla* and its symbiont *Anabaena*, which lives in tiny pockets in the *Azolla* leaf. When the fern germinates and pushes its way out of the spore, the tiny plant picks up its symbiont as it grows past the pocket. As the plant forms, the *Anabaena* culture establishes itself in its new home, ready to spread to all the developing fern's leaves.

This ensures that each *Azolla* plant is well-stocked with *Anabaena*, but it makes it difficult to envision improving the symbiont by tinkering with the algal partner. "Even if we could develop a super strain of *Anabena* it may be very hard to get it into any *Azolla*," says Calvert. Nonetheless, *Anabaena* is still a useful system in which to study the molecular genetics of nitrogen fixation.

STI nitrogen fixation research has profited greatly from the exchange of biological samples between United States and Indian laboratories. "There is no doubt that this will aid our effort," says Marvin Lamborg, who coordinates Battelle-Kettering's involvement in STI. "The greater the diversity of the materials, the more tools we have to search for mutants."

STI has also given researchers a chance to get a better perspective on the problems that are important to farmers. "We've learned a lot about the practical aspects of agricultural research in India," says Helinski. "That gives us a better appreciation of the work their scientists are carrying out."

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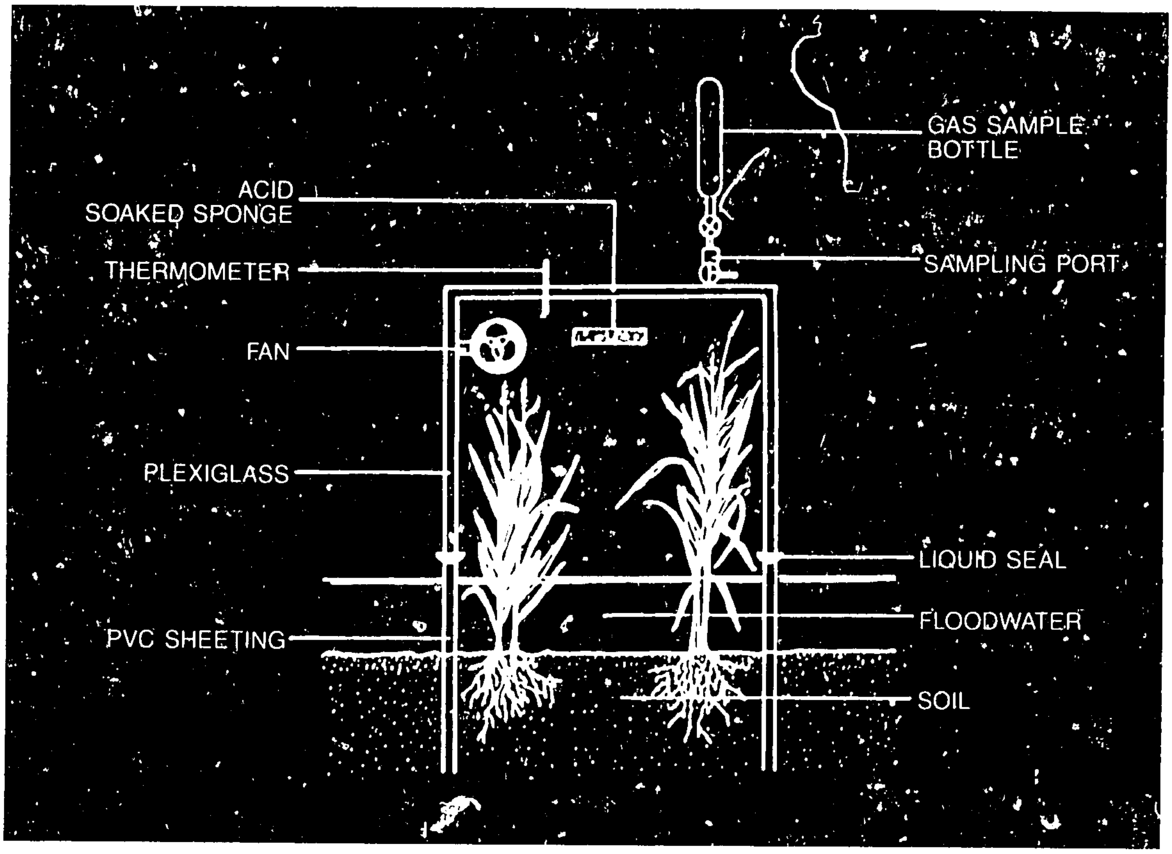


Since at least half the fertilizer applied to agricultural fields now goes to waste, STI researchers are trying to understand those losses. Rice plants, for example, utilize as little as 20 percent of the available nitrogen; some gets converted into gases like ammonia, nitrous oxide, or nitrogen and wafts into the atmosphere. An essential technique for measuring nitrogen losses involves augmenting the amount of Nitrogen-15 in fertilizer, then measuring that isotope's concentration in plants and the surrounding water, soil, and air in a closed environment like this one.

The Case of The Disappearing Nitrogen

Instead of applying more fertilizer, one answer to more efficient farm production is to make better use of what's already there.

by Tom Alexander

The United States and India have a lot to learn from each other about agriculture. Until recently, the exchange was mostly one way—from the United States, whose greatest claim to a place in history may rest on its achievements in harnessing science to agriculture. For example, the two-decade-old Green Revolution that has helped transform once-hungry, food-importing Third World countries into self-sufficient grain exporters was largely an offshoot of the United States's own on-going agricultural revolution.

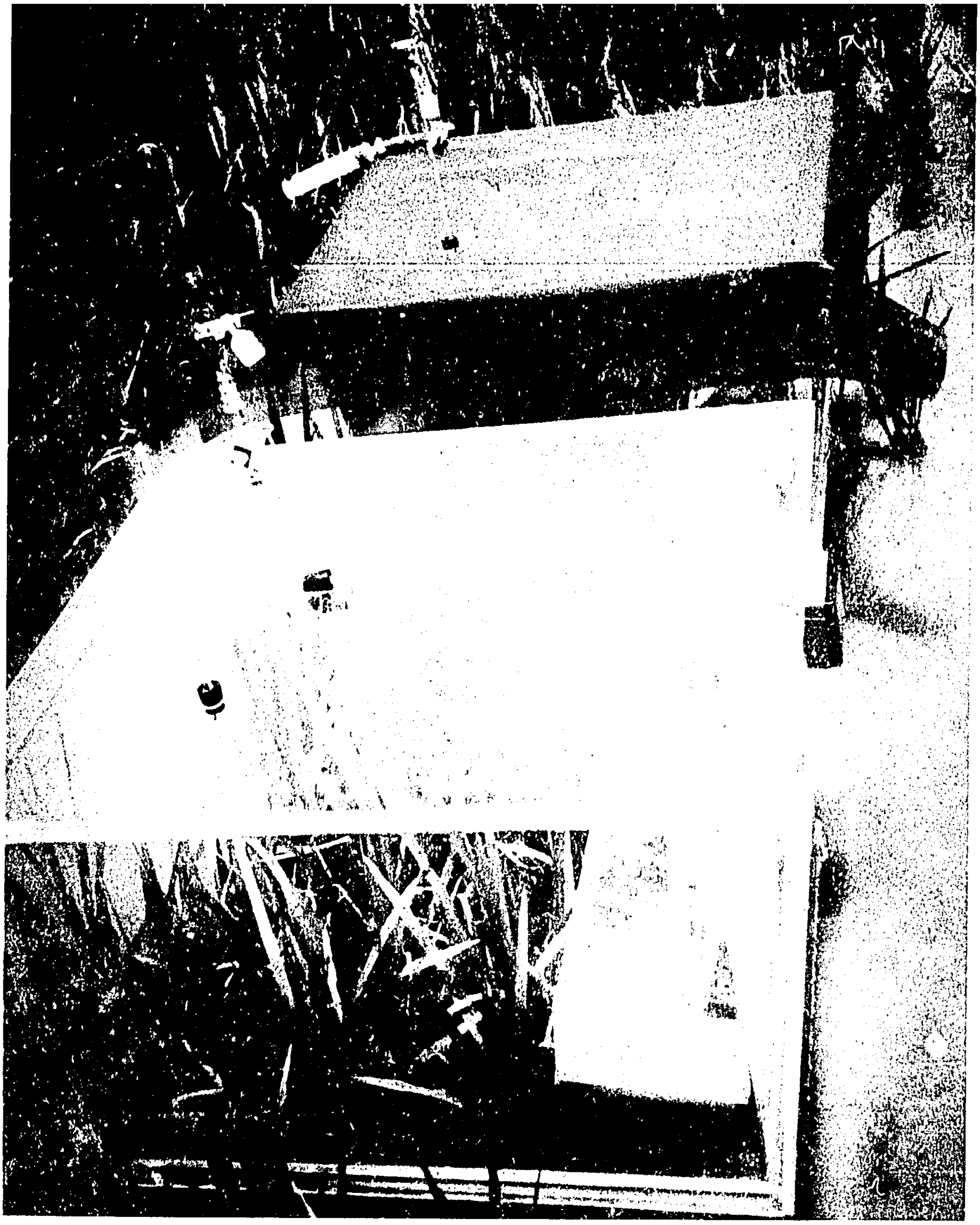
Under the Indo-United States Science and Technology Initiative's agricultural program, the exchange is more of a two-way street. While the United States may still have an edge in high-technology farming, it can learn a lot about economic efficiency from both the new science and ancient practices of agricultural India.

Cultivated for many thousands of years, Indian lands have long-since been depleted of topsoil and natural nutrients. They are often farmed with minimal amounts of chemical fertilizers, herbicides, and pesticides, sometimes under weather conditions that would be termed severe drought in the United States. In these circumstances which would provoke despair in an American farmer, his Indian counterpart often manages impressive outputs and five or six crops a year.

The earlier agricultural revolution in the United States and the later one in India both hinged mostly on chemical fertilizers. United States fertilizer use jumped enormously after World War II, in part because the great wartime plants that had produced nitrate-based explosives were converted to produce nitrate fertilizers instead. The principal innovations in Asia's Green Revolution in the mid-Sixties were rice and wheat strains that responded well to those nitrogen fertilizers. Now, however, there is considerable worry that food production in countries such as India will once more fall behind the current population growth-rate of 2.5 percent a year.

Up to a point, each additional pound of applied nitrogen produces roughly ten additional pounds of wheat or rice—so more fertilizer would obviously help forestall the grim prospect of food scarcity. But fertilizers are energy-intensive products, manufactured largely from natural gas or petroleum feedstocks. Energy costs already represent the heaviest economic burden for many Third World countries. Nowadays, every pound of nitrogen in fertilizer costs about 30 cents. For highest yields, scientists recommend that farmers apply 120 to 150 pounds per acre each year. Unfortunately, the $35 to $45 cost is generally unfeasible in countries like India where per-capita incomes average only $200 or so and where the total market-value of an acre of crops may amount to only about $25.

The average American farmer customarily applies a lot more fertilizer than his Indian counterpart, but in recent years he too has come under heavy pressure. The main farm problem in the United States is too much production and too low prices, so farmers here also suffer economic hardships. One promising way around high fertilizer costs lies in increasing fertilizer efficiency. At least half the fertilizer now applied simply goes to waste. Depending on farming practices and other factors, rice plants may



Rice plants grow in air-tight boxes near Crowley, Louisiana, in an STI experiment to measure how much nitrogen from fertilizer gets lost into the atmosphere.

recover as little as 20 percent of the available nitrogen. "We believe that could be increased to 70 percent if we understood factors controlling the losses and change farming methods to compensate," says John Malcolm, a plant physiologist and fertilizer expert with the United States Agency for International Development. Malcolm coordinates United States research on nitrogen fertilizer efficiency under STI.

Where all the wasted nitrogen goes is a matter of some dispute and intense research. It's clear that some simply gets washed away and or leached into groundwater supplies by rain or irrigation waters, some gets converted by chemical and bacterial action into gases like ammonia, nitrous oxide, or nitrogen and wafts off into the atmosphere.

The goals of STI nitrogen fertilizer research include discovering what soil and water conditions and agricultural practices foster these losses and devising ways to stem them. M. C. Sarkar, a soil scientist at the Indian Agricultural Research Institute near Delhi, says that even if Indian fertilizer losses were reduced by just five percent, they would increase both plant growth and the average farmers' willingness to use more fertilizer and thereby make a hefty difference to the food economy.

An essential research technique Western scientists have devised to trace nitrogen losses involves the use of the isotope Nitrogen-15, ^{15}N. It normally makes up 0.37 percent of the nitrogen found in nature, the remainder being ^{14}N. In their experiments, researchers use special batches of fertilizer in which the proportion of ^{15}N has been augmented to five percent. Non-radioactive and chemically-identical to ^{14}N, ^{15}N is nevertheless detectable with instruments called mass spectrometers. So, by applying the enriched fertilizers and measuring the ^{15}N concentration later found in plants, as well as in the water, soil, and atmosphere of the plants' environment, researchers can estimate where the fertilizer goes. One aspect of the STI program entails introducing Indian scientists to the ^{15}N technique and equipping them with mass spectrometers.

To be sure, the technique has some drawbacks. In the first place, Indian scientists are finding it to be almost prohibitively expensive. The enriched test fertilizers cost over $3,000 a pound, so they can only be used in laboratory-scale experiments on a few plants, which don't necessarily reflect real-life farming conditions. Moreover, even a minor electrical fluctuation—which is common in the Indian power system—generally wipes out a mass-spectrometer measurement. Finally, there's considerable controversy about the technique's reliability at best. John Duxbury a Cornell University agronomist finds that certain soil micro-organisms routinely replace some of the ^{15}N in fertilizers with ^{14}N from soils, thereby confusing the measurements. Working under an STI grant, Duxbury and his colleagues are trying to calibrate this effect.

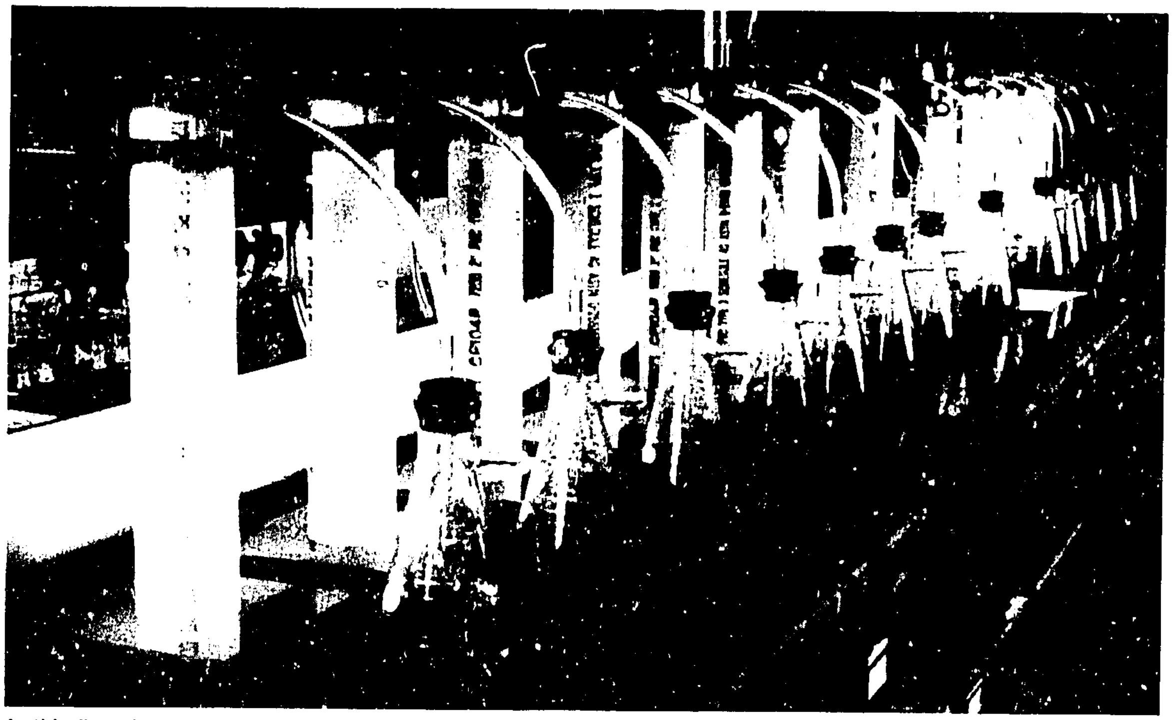
Where researchers do agree is that blanket recommendations to all farmers about how to improve nitrogen efficiency probably won't be valid. The amounts and avenues of loss seem to depend on many variables like crops, soil-types, irrigation practices, rainfall, and temperature. Soil scientist Richard Fox and his colleagues at Pennsylvania State University have found, for example, that applying urea—a cheap source

The ultimate answer might be a computer model into which farm agents feed facts about plant species, soils, and climate and out of which pops advice about farming under those conditions.

of nitrogen commonly used in Asian agriculture—to moist soils dramatically increases nitrogen loss. Somewhat paradoxically, however, the Penn State researchers also find that, in the case of dry-land crops like wheat, the very best time to apply urea is a couple of days before a heavy rain. That discovery underscores the importance of STI efforts to improve weather forecasts. On the other hand, rice researchers like William Patrick at Louisiana State University find that growing rice in continuously flooded paddies wastes less nitrogen than in intermittently flooded paddies. One tactic that may reduce losses is holding off fertilizer applications until crops enter their period of maximum growth.

James Powers, leader of an STI project in the United States Department of Agriculture's research service in Lincoln, Nebraska, suggests that the ultimate result of fertilizer efficiency research might be a computer model into which farm agents could feed local facts about things like plant species, soils, climate and so forth, and out of which would pop advice about farming under those conditions—the types and amounts of fertilizer to apply, timing and depths to apply it, for example. Toward this end, STI researchers are running ^{15}N tests in widely varying soils and climates—in New York, Pennsylvania, Louisiana, Colorado, Nebraska, and California in the United States as well as in Uttar Pradesh, Punjab, Orissa, and Tamil Nadu in India. Researchers from both countries routinely visit each other's labs for insights.

One idea borrowed from outside both countries involves packaging fertilizer in different forms. Scientists recognize that burying fertilizer in the soil not only inhibits its run-off but also reduces exposure to oxygen and thereby slows formation of ammonia and other gaseous compounds. In



In this flow-through experiment at Penn State, Richard Fox measures the amount of ammonia that is lost from fertilizer. Air flowing over fertilizer mixed with soil in the white pipes bubbles into flasks containing boric acid. Researchers then measure how much ammonia is trapped in the flasks.

China, peasant families have long spent their winters rolling fertilizer-enriched mud-balls, which they later implant deep in the ground between hills of rice. Taking a cue from this, researchers at the Tennessee Valley Authority have devised moth-ball-sized fertilizer pellets designed to slow the release of nutrients, like the "tiny time pills" familiar in TV commercials. Now, fertilizer pellets are also being coated with sulfur or mixed with other chemicals designed to inhibit the nitrogen-wasting reactions that occur underground. While all these products are being tried out in both the United States and India, and while they seem to work, researchers in both countries fear they may cost more than the fertilizer they save.

Indian farmers probably stand to benefit most from STI research on artificial fertilizers, but American farmers may gain from Indian practices that reduce fertilizer requirements altogether. In most sections of India, especially those where several crops a year are the norm, farmers generally practice intense forms of crop-rotation—planting, for example, one or more rice crops during the summer monsoon, wheat in the fall and finally legumes or other "green manure" crops that add both nitrogen and organic material to lighten soil and help retain moisture. Crop-rotation and green-manuring was once common in the United States, too, but largely fell out of favor as the post-war era of cheap fertilizers seemed to make them unnecessary for good yields.

Recently, they have been returning to favor in the United States. Farmers see them as ways to reduce fertilizer costs. Agricultural scientists believe that in the long run artificial fertilizers and single-crop monocultures probably exact a heavy price in soil-damage. United States lands like the Great Plains bread basket have been under cultivation for less than a century but have already lost roughly half their valuable topsoil and organic nitrogen and trace-nutrients, partly because of heavy tillage, erosion, and farming methods that don't restore organic materials. Moreover, United States society as a whole has a stake in reducing erosion, energy consumption, and overuse of agricultural chemicals that wind up polluting groundwater, lakes and streams. Many argue that these social values might

Instead of turning green manure under when it ripens as is the American practice, Indian farmers generally leave it on the surface where it helps hold water and reduce erosion.

justify subsidies to farmers to encourage other practices.

James Powers and his United States Department of Agriculture colleague, plant physiologist Wallace Wilhelm, have returned from STI-sponsored visits to India impressed by the low-tillage green manuring they found. "They have been working those fields very hard for thousands of years," Wilhelm points out, "We're trying to learn from their old mistakes and current practices." Specifically, he and Powers are trying to adapt those practices to American conditions, estimating that Great Plains corn farmers might reduce fertilizer use by 25 percent and improve soils by sowing legume cover-crops such as peas, beans, or vetch after the corn harvest.

Instead of turning this green manure under when it ripens as is the American practice, Indian farmers generally leave it on the surface, where it helps hold water and reduce erosion. Powers and Wilhelm believe this would be advisable in the United States as well. They acknowledge that such no-till experiments with corn and soybeans show that leaving crop residues on the ground roughly doubles crop output and efficiency.

Agricultural problems and priorities in India and the United States are, by and large, quite different. In India, the problem is increasing output to keep pace with the expanding population. In the United States it's chiefly minimizing soil deterioration and holding down costs so that farmers can stay in business. What's impressive about the cooperation fostered under STI is that it seems to be advancing both those ends.

Tom Alexander is a freelance writer based in Washington, D.C.

Many Indian households spend up to 14 person-hours a day collecting wood for fuel and in the process destroy forests, harm agricultural and mountain lands, and even change weather patterns.

Social Forestry Serves the Villages

The answer to the world deforestation crisis may be grass-roots plant programs, but first science must lend a hand.

by Tom Alexander

Each year, the world loses some 50 million acres of forest, an area half the size of California. At that rate, by the year 2,000, 40 percent of the remaining forest-cover will be gone. Most of the disappearance occurs in the tropics, especially in poorer countries, where the main energy-source of the relentlessly-growing populations is firewood and where the pressures for more land for agriculture and animal-grazing are most intense.

In destroying local forests, unfortunately, people destroy their livelihood, as the case of India makes clear. "India is not Bombay or Delhi or Calcutta," says T.N. Khoshoo, an ecologist who recently retired as Secretary of India's Department of the Environment.

"India is mainly 576,000 villages—far-flung, often inaccessible hamlets of from four to ten houses. If you go to one of these villages, you'll find a biomass-based society and economy. Virtually all the fuel, food, fiber, fertilizer, shelter, and medicine has its origins in local plant-life." Already, many Indian households devote up to 14 man-hours a day, or 35 percent of the family income, to obtain fuel. By the year 2,000, according to various estimates, demand for firewood will exceed the supply by some 25 percent and there's little prospect that substitutes will be found.

The forests' disappearance represents far more than a village energy crisis; it lies at the center of a spiral of events that ultimately affect the entire world. In semi-arid lowland regions such as much of northern India, the quest for fuel leads people to burn the animal dung and crop wastes that are their best sources of fertilizer and moisture-holding organic mulch. So, agricultural soils deteriorate, animal grazing outruns plant growth and begins to damage roots, and finally people move on to repeat the process elsewhere. According to some theorists, many of the world's deserts, including the Rajasthan in India, are man-made products of this process. Some believe that desertification is also self-amplifying: once it starts, it often alters local climates to reduce rainfall.

In mountainous regions like the Himalayas, destroying vegetation eliminates the main control over erosion; slopes and entire villages wash away, and silt fills the rivers and the dams that control flooding and supply irrigation and electricity for hundreds of millions of people throughout Nepal, India, and China. Hundreds of miles downstream, in great flood-plains like the Ganges where more hundreds of millions reside, the silt-choked rivers broaden out to inundate hundreds of villages and cities, sweep away croplands or water-log them into infertile hard-pan soils caked with salt or alkali. So people are driven away to slash and burn still more forest lands.

Nor are far-off wealthier countries immune from the consequences. Over the long run, there's no prosperity but general prosperity: poverty and distress, wherever they occur, render debtor nations insolvent, depress trade, destabilize political systems, foment international strife. More ominous than the economic are the environmental implications: the world's forests represent a primary reservoir for carbon dioxide, a gaseous product of combustion. When forests are thriving, they help absorb carbon dioxide from the industrial world's prodigious

A social forestry experiment now underway in India begins with 10-inch cuttings of various species of American poplar. Planted in nurseries, they quickly sprout to yield more cuttings for large test plots.

burning of fossil fuels that took many millions of years to accumulate. But when forests burn or decay, they contribute still more carbon dioxide to the atmosphere. Like the panes of a greenhouse, the blanket of gas inhibits the radiation of heat from earth, allowing temperatures to rise and change the fundamental dynamics of weather. Some meteorologists believe that the rapid carbon dioxide buildup in this century has already begun altering the global climate. As a rule of thumb, any climate change can be considered bad, at least in the short run, for man, for his institutions are tuned to precisely the climate that prevails.

The United States has participated in many programs to stem the forests' decline, while India has ambitious re-forestation projects underway of its own. The biomass project of the Indo-United States Science and Technology Initiative seeks to raise the contribution science can make to these efforts. Because India has plenty of cheap labor to help with the labor-intensive planting experiments, it can serve as a kind of laboratory to explore techniques of reforestation in other tropical countries. About half a dozen research institutions are participating on the United States side, led by Stanley Krugman, a plant geneticist with the United States Forest Service in Washington. Roughly the same number of organizations is involved on the Indian side.

India's central government and individual states have been carrying out tree-planting programs for many years, planting both commercially-valuable lumber species like teak and sal in large plantations, and species like eucalyptus on roadsides and other areas to provide fuel and help restrain erosion. Recently, however, afforestation has risen to top national priority, particularly since the Green Revolution has lessened concerns about food.

India proposes to plant trees or shrubs on five million hectares—roughly 12.5 million acres—each year. The main target areas are Himalayan mountains and foothills and the over-grazed, farmed-out, mined, arid, or waterlogged wastelands that constitute about a third of India's total area. The aim of this social forestry is to control runoff and

After cuttings sprout limbs, Indian workers chop them up to provide more cuttings.

supply fuel, fodder, and minor forest products, plus vocations for hundreds of millions of people in the villages. In addition, the trees will generate humus, possibly help fix nitrogen into soils, and absorb crop-damaging salts and other minerals. So there's hope that over the long-term, present wasteland will be reclaimed for agricultural uses.

So far, India's tree-planting efforts have met with mixed success and considerable controversy. Demands by people for food and firewood and by cattle for grazing have outpaced afforestation efforts, so net forest cover has continued to decline. According to satellite surveys, India lost nearly three percent of its forest cover in the seven-year period between 1975 and 1982. Forests now cover only 14 percent of India's net land area, and almost all of them are government-owned.

The ambitions of planting 12.5 million acres a year are constrained in part by uncertainty over what kinds of trees to plant. The climate and soils of India vary about as widely as those in the United States, so species compatible with the various conditions must be found. Once they are, enormous logistical problems remain in producing billions of seedlings each year and getting them all planted. STI's biomass program exists mainly to address these issues: to discover or develop hardy, fast-growing trees or shrubs suited to Indian growing conditions; to devise technologies for mass-producing seedlings; and to perfect low-cost planting and tending techniques appropriate to villagers and farmers.

Hitherto, the main tree of choice in India's social forestry program has been eucalyptus, the gangly, leafy, pungent-smelling evergreen that, in the United States, is mainly found in California. Native neither to India nor the United States, eucalyptus came

Once fertile ground, this barren wasteland near Lucknow has been overgrazed and waterlogged.

originally from Australia. It was first planted in India nearly 200 years ago in the palace gardens near Mysore. A hybrid version of these early Mysore plantings is now the most widely planted tree in India. Eucalyptus grows rapidly and, in its various species and varieties, adapts to a wide range of conditions, particularly the arid conditions that prevail for most of the year throughout most of India. It can't tolerate much cold, nor, because of its brittle branches, heavy snow-falls. It also doesn't do well in alkaline soils. But its dense wood makes excellent fuel and can be used for paper, poles, and certain kinds of lumber. Thanks largely to government planting programs, eucalyptus now seems to dominate India, visible along roads almost everywhere.

For all its successes, eucalyptus is incurring growing animosity from Indian environmentalists and others. Many resent the way government has pushed the exotic tree over indigenous species, some of which grow just as rapidly. Cooks often deplore the taste eucalyptus smoke imparts to food. And many scientists now acknowledge that its extensive tap-root system and year-round leaf canopy transpires lots of soil moisture, lowering water tables during dry seasons.

Critics also contend that, on balance, eucalyptus harms more than helps the soil, by robbing it of nutrients. While eucalyptus will probably continue to be planted in India's program, an intense search is now going on around the world for other genera and species than the almost haphazardly-collected ones that have been planted up until now.

In the first phase of the STI program, Indian and American participants have scoured their respective countries and much of the world at large both for better species already being planted as well as for genera that have been overlooked entirely. The researchers are exchanging samples of their collections of fast-growing trees and shrubs derived from a wide range of climates and soils. Under the leadership of Thomas Leddig of the United States Institute of Forest Genetics in Berkeley, California, STI is collecting and shipping American eucalyptus samples for trials in India. Other institutions send over samples of pine, poplar, and other trees and shrubs. One of the odder exports, directed by Joe Goodin of Texas Tech University's Arid Lands Institute, involves *Atriplex canascensis*. Commonly known as salt-bush, it's a pesky shrub that thrives in the

Planted in 1983 on hardpan soils, these poplars from American stocks thrive in conditions very different from their verdant, native habitat.

A.N. Chaturvedi, director of the Indian poplar experiment, examines newly-planted poplars on near-barren alkaline wasteland typical of much of India.

One of the odder exports is salt bush, a pesky shrub that thrives in the most appalling soils and climates throughout much of the American West, where it makes good fuel and cattle feed.

most appalling soils and climates throughout much of the American West. It makes good fuel, and cattle find it edible.

America may also benefit directly from this search. Most of the trials in India are being duplicated on United States soils, and India has already shipped samples of its Mysore eucalyptus. It's worth noting that most commercial forestry in the United States is based on native species, while North American agriculture is primarily based on exotics. Even "typical" American plants like potato and maize actually originated in Central and South America, and most other vegetables and grains came from regions even more remote.

There's good reason to suspect that the STI project will turn up trees more suitable than those now being planted. Botanists recognize some 500 species and 138 named varieties of eucalyptus alone, for example. Beyond that, there's a countlessly larger number of unnamed minor populations that have adapted themselves to specific conditions. Finally, individual trees within these populations, like individual horses or humans, differ considerably, so the hunt is on for superior individuals as breeding stock for superior progeny.

At the moment, some Indian foresters are enthusiastic about American poplar, with which Krugman has had almost 20 years of experience, as a candidate to replace much of the ubiquitous but controversial eucalyptus. India's few native poplar species grow only in the Himalayas. In the United States, by contrast, poplar in its many species and varieties is found the length and breadth of the land. Aside from their adaptability, American poplars are among the fastest-

In a well-established poplar plantation in the state of Uttar Pradesh in north central India, researchers number individual trees from different populations to learn which grow fastest in that habitat. Wheat thrives between the trees, giving farmers an inexpensive way of growing additional crops.

growing trees known; in average soils and with minimal care, some species grow 75 feet or more in eight years. Poplar also is easy to breed and plant. The pollen from a male of one poplar species will generally fertilize blossoms from females of many other species, producing hybrid offspring embodying desirable characteristics of each. All that it takes to plant poplar is to stick a green cutting in the ground and keep it watered for a while.

Though poplars grow straight and tall, their wood is lightweight, softer and less decay-resistant than most timber species. Hence, it's suited best for use in matches, crates, fibreboard, paper, and lumber that isn't exposed to heavy stresses or weather—cabinets and other light furniture, for example. As firewood, it doesn't produce as much heat as heavier woods like eucalyptus, which some consider a drawback in social forestry. But Edward Hansen, of the United States Forest Service's experiment station in Rhinelander, Wisconsin, and leader of the American side of the STI poplar project, argues that poplar has compensating qualities. "Poplar may not produce as many BTUs per pound as other woods," says Hansen. "But since it grows so fast, the actual energy production from a given piece of ground is greater."

Under Hansen's leadership, several institutions throughout the United States collected specimens of ten poplar species and varieties. Hansen shipped 165 cuttings—green sticks about ten inches long—of four American poplar species to a forest experiment station in the Himalayan foothills. There, the cuttings were planted, and after growing to a height of six feet or so in their first season, their branches were trimmed and chopped into still more cuttings. By this means, within a couple of years, one cutting yields enough material for approximately a hundred plantings, some of which are being distributed to other test sites in India.

In one form or another, American poplars seem to grow almost anywhere. In early 1986, Hansen visited an Indian Forestry Department experimental plantation near Lucknow, where test-plantings are underway in worn-out, over-grazed, hard-pan, semi-deserts typical of many Indian wastelands. He was surprised to find one poplar, *Populus deltoides*, (often called eastern cottonwood in the United States) from Stoneville, Mississippi, thriving in arid, alkali-caked soils like nothing known in Mississippi.

Another discovery from the Indian experiments may provide the answer to the enormous problem of planting all those trees that India contemplates. The foresters generally fence off their experimental plantations to keep India's ubiquitous, free-ranging cattle from eating or trampling the seedlings. Since the seedlings are irrigated during early growth stages, tall grasses often spring up and compete with the young trees. Reluctant to acquire tractors and mowing machines, the experimenters began allowing local farmers to cultivate crops between the tree-rows on condition that they don't damage the seedlings and keep the grasses down. Most of the crops did well, some even better than in the farmers' own fields. In India's sunny clime, apparently, a touch of shade is just the ticket for many crops, particularly leafy vegetables grown in the scorching spring before the summer monsoon. The deciduous poplar, which doesn't leaf out fully until late spring, appears to furnish just the right amount of protection, particularly if some of its branches are pruned. Meanwhile, of course, the shedding leaves enrich the soil.

As soon as word got around, local farmers clamored for the opportunity to plant on the forest-service lands. "At first we didn't charge them anything," says A.N. Chaturvedi, director of research at the Uttar Pradesh Forest Department and manager of the Lucknow experiments. "Then we raised the fee to a rupee per hectare per season. Now, we're charging 70 to 80 rupees." (One rupee is worth about eight cents.) Now, farmers in north India are trying to buy poplar seedlings for their own fields. The prunings provide fuel for local communities and sometimes additional income for the farmers. In fact, many Indian farmers have discovered they can make more money farming trees than conventional crops. One thriving outlet is the paper industry: India currently imports much of its pulp from Europe, and paper is expensive.

India's recent experiences with market incentives of this sort has stimulated an enthusiasm for "agro-forestry" as the answer to the problem of how to get its ambitious tree-planting done—relying more on private and village initiatives and less on expensive, often controversial, government planting programs. "It's only when we benefit the individual farmer that we can benefit India as a whole," Chaturvedi says.

Because of their rapid growth, poplars seem an ideal candidate for the Indian innovation known as short-rotation forestry. After six or seven years, when the trees reach a diameter of six to ten inches and are over their period of maximum growth, they will be cut for firewood, pulp, or lumber, and the planting process will start all over. Some United States investigators are closely following India's short-rotation experiments with poplar for possible translation to American conditions.

Of course, short-rotation forestry only augments the problem of supplying planting material. Even if nursery- and planting-stock takes the form of cuttings, as in poplar's case, it would take years to grow enough material for a single year's planting under India's ambitious afforestation program. In particular foresters would like to be able to plant only identical offspr' ıg of selected "elite" trees. Rapid production will become vital if researchers ever master techniques of "bio-engineering" trees through gene-splicing

"Poplar may not produce as many BTUs per pound as other woods, but since it grows so fast, the actual energy production from a given piece of ground is greater."

techniques. It might, for example, become posible to provide poplars with the same genes that give the salt-bush its special tolerance for salt and lack of moisture.

Indian botanists now rank among the world's most adept at the tricky art of cloning trees from cultures of plant tissue. Pioneer laboratories in the techniques include the National Botanical Research Institute in Lucknow and the National Chemical Laboratory at Pune. Dating back some thirty years, their efforts first met success with orchids and other commercially-valuable flowers. About a decade ago, they succeeded in the more difficult task of cloning woody plant-tissue, namely commercially-valuable fruit trees.

Essentially, the process involves subjecting a few cells from a seed or growing shoot to a precise combination of growth hormones and nutrients at certain stages in the plant's growth cycle. Then, the culture is sterilized and transferred to an artificial growth medium and allowed to grow under carefully-controlled conditions of light and temperature. At a certain stage, the cloned material may be packaged inside a nutrient capsule as a kind of synthetic seed, plantable like any other. Sometimes, though, the culture is incubated until it reaches the size of a miniature seedling, at which point it is transferred to a nursery, and raised as a mother tree, from which more nursery stock is cloned.

Proud as they are of their tissue-culture successes, the Indians defer to the American genius for mass production. "India has made the largest contribution to the science of tissue-culture," says Khoshoo. "We see America's role as helping convert that science into a technology."

Tom Alexander is a freelance writer based in Washington, D.C.

MONSOON

Before the monsoon, women seek shelter from winds that whip across Rajasthan.

Weathermen Take a New Look at "Teleconnections"

With the goal of predicting monsoons, United States and Indian researchers are investigating the links connecting weather events half a globe apart.

by Tom Alexander

In certain respects the summer monsoon is the world's most reliable meteorological event: it happens every year within two weeks of a given date. Nevertheless, the monsoon's remnant unpredictability presents a serious problem for the roughly half of mankind whose survival is critically tuned to its signal. For it brings the deluging rains that transform vast portions of Asia, Africa, and Australia that would otherwise be near-barren lands into fruitful larders for some two billion of Earth's inhabitants. When it falters, as it has from time to time throughout history, multitudes starve, conflicts rage, nations totter. For a century, now, meteorologists in India have sought to predict the monsoon, with a view to maximizing its beneficence and minimizing its malevolence.

Now, under the Indo-United States Science and Technology Initiative, these Indians are being joined by American researchers who have an intense interest in understanding monsoons. Tropical weather systems and particularly monsoons are now seen as major agents in the transfer of the sun's energy falling in equatorial regions to the mid latitudes, with powerful effects on the weather there. "The monsoon helps fuel the world's atmospheric engine," says M.C Sinha, a researcher at the Indian Meteorological Department in Delhi. "Medium and long-range forecasts of weather anywhere in the world will have to take it into account."

The STI monsoon research is divided into two programs. Program I aims to improve and extend short-range forecasts of the monsoon onset in various regions of India, as well as the timing and duration of monsoon breaks, the dry spells that alternate with rainy spells throughout the monsoon season. Program II is both more basic and more sweeping: it is striving for sufficient understanding of world-spanning weather-producing systems to predict, months or perhaps years in advance, whether future monsoons will produce more or less total rain than normal.

Currently, India's weather forecasters generally provide short-range (two- to four-day) predictions of the arrival of monsoon breaks and rains in a given region with fair accuracy. But they believe that with very large computers and worldwide data, seven- to ten-day forecasts are possible. Such medium-range forecasts would enormously benefit Indian farmers. Typically, for example, Asian rice-planting is a weather-dependent two-step process. During the hot, dry season from April to June, farmers sow rice in tiny seed beds irrigated by wells or carefully-hoarded rainwater supplies. Once the monsoon rains arrive, farmers quickly transplant the sprouted seedlings into larger paddies kept flooded by the rains. Unfortunately, farmers can't always be sure just when the monsoon has truly arrived; it can vary by up to a month and is often preceded by weeks of intermittent storms, or false monsoons. But once seedlings are in the paddy, they are vulnerable: unless kept flooded, yields are greatly reduced, while two weeks without rain may be enough to ruin the crop.

By careful planning based on weather expectations, farmers sometimes harvest as many as six crops a year from their limited acreage. Better knowledge of monsoon breaks also improves the efficiency of fertilizers and pesticides. (See article beginning on page 51.) Long-range predictions would provide other benefits: if, for example, farmers have reason to believe that the coming monsoon rains are likely to fail—i.e., to be skimpy—they might elect to plant drought-resistant strains of rice or even forego rice for less-thirsty crops, like wheat or millet.

Long-range forecasts would be of inestimable value to government planners. Critically dependent as it has always been on the feast or famine of monsoonal weather, India has over the centuries devised elaborate water-management policies to control disastrous floods and channel them into large combined irrigation and hydroelectric reservoirs or small tanks or farm ponds. About half of India's power is water-generated. Depending on the amount of rainfall anticipated, water may be deliberately released or rationed to the point of reducing crop yields and promoting blackouts. Planners would also like to anticipate nationwide agricultural yields in order to set export and import quotas for food, quotas that will maximize foreign exchange without pinching domestic supplies.

Like most weather phenomena, monsoons are driven by temperature differences: in essence, they represent nature's attempts to equalize these differences. They also represent a modification of the tropical pattern of air circulation first speculated on by the 17th century geophysicist Edmund Halley and worked out in detail in 1735 by the British lawyer and philosopher George Hadley. Hadley suggested that the direct rays of the sun warm the sea surface at the equator, heating the atmosphere and causing the warm air to rise. The rising air cools, causing its moisture to condense and fall as rain in the tropical regions. Then, like air rising above a radiator and spreading along the ceiling to cooler walls, the now-dry equatorial air proceeds northward and southward about a third of the way to the poles and descends. In descending, the dried equatorial air creates the arid high-pressure belts—the desert regions of Africa and Arabia, northern India, Australia, and Central America. Part of this air returns to the equator, the rest continues polewards.

Like most weather phenomena, monsoons represent nature's attempts to equalize temperature differences.

When the equatorial air rises and begins to move poleward, it carries with it the speed induced by the earth's west-to-east spin. At the equator itself, this amounts to about 1,100 miles an hour, while at the pole, the rotational speed is zero. Air returning from the mid latitudes has less velocity than at the equator and therefore takes the form of winds blowing from east to west—the trade winds that swept sailing ships across the Pacific to the Orient in years gone by. In honor of its discoverer, this tropical movement of air is known as Hadley circulation, and the convecting volumes of air as Hadley cells.

Hadley invoked a mini-version of the global convection pattern to explain monsoons. As the northern hemisphere tilts toward the sun in late spring, tropical land masses there heat up rapidly. The land warms more rapidly than the adjacent seas, partly because less energy is needed to heat soil than water, and partly because deep cold water mixes with the warm surface water. In southern India, by late May or early June, the sea-land temperatures differ enough to trigger a giant version of the sea breeze that cools sunbathers on hot afternoons at the beach. Air rising from the hot land produces a low-pressure region drawing in moist air from the adjacent seas. As this moist air reaches the hot convection zone and begins rising, it cools and loses moisture, producing the three-month-long monsoon rains of Asia, similar to the brief thunderstorms of a coastal summer afternoon.

Conventional forecasting techniques that

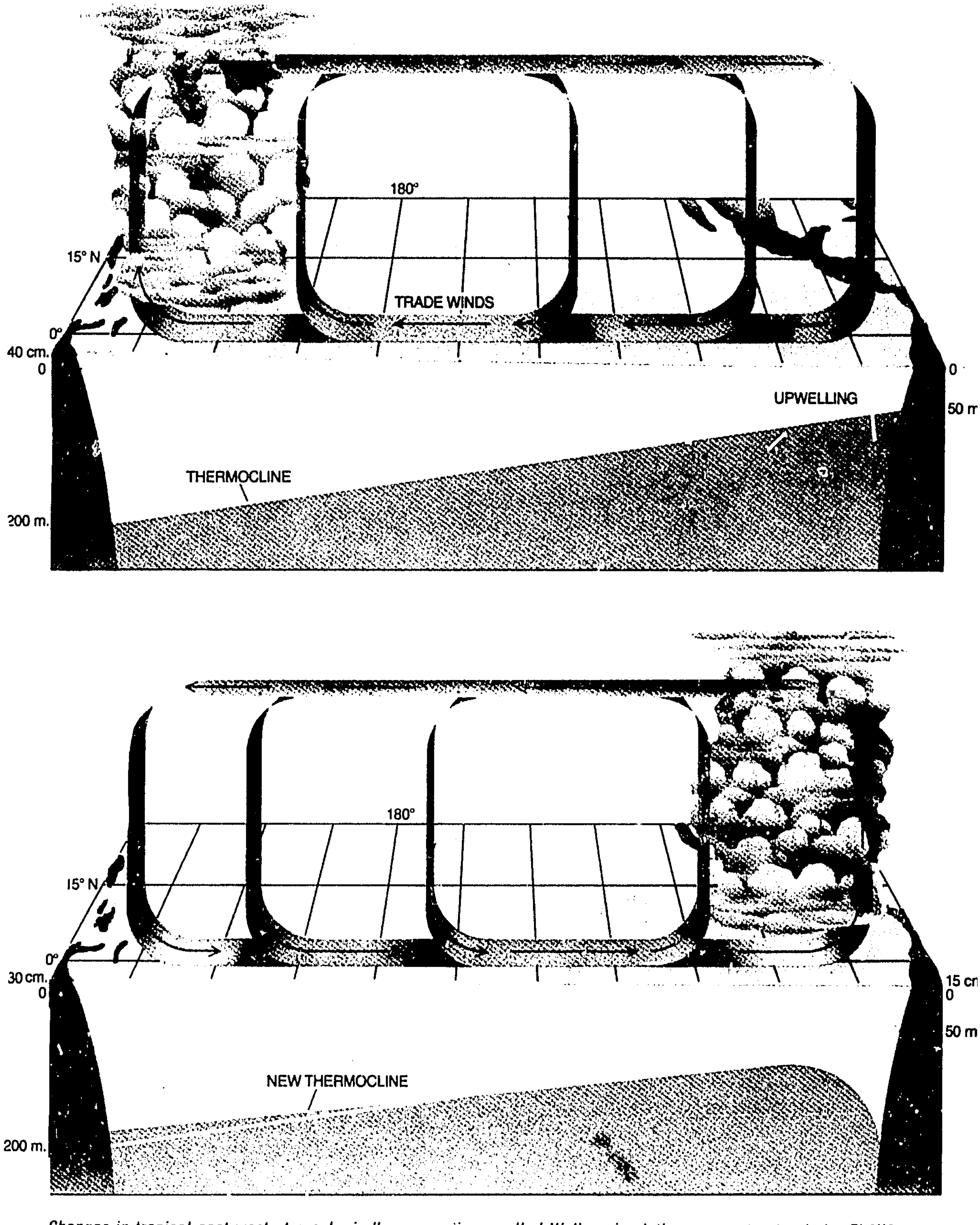
On India's west coast a farmer rejoices in the refreshing monsoon rains as he and his water buffalo prepare the soil for the transplantation of rice seedlings.

attempt to plot movements of air masses on weather maps don't work as well on tropical and monsoon flows as they do further north. As the monsoon progresses northwards across India, its movement becomes complex and erratic. Some meteorologists suspect that short- and medium-range monsoon forecasts will always be less reliable than weather forecasts further north. Furthermore, any attempts to forecast more than one or two days ahead—whether in the tropics or the higher latitudes of either hemisphere—probably must abandon the weather-map approach in favor of computerized calculations using worldwide data. Since both the United States and India want to improve forecasts in the seven- to ten-day range, their respective needs are a major rationale for the STI cooperation, according to Pamela Stephens, a meteorologist with the United States National Science Foundation and monsoon project manager on the United States side. "The Indians need our modeling expertise, and we need their experience and accumulated knowledge about the monsoon," says Stephens.

While short- and medium-range forecasting of monsoon rains may be harder than mid-latitude forecasting, long-range monsoon forecasting may in many respects be easier. This important perception was sensed long ago in India. In April, 1986, in fact, many of the world's meteorologists met in New Delhi to commemorate the 100th anniversary of long-range forecasting in India. After monsoon failures in 1877 and 1899 brought devastating famines to the country, the British colonial government sought advance warnings of future failures in the hopes of improving the management of water and food-stocks. Colonial meteorologists pioneered the view of weather as a global mechanism full of "teleconnections" by which far-off events influence local outcomes. This global perspective is now one of the dominant themes in modern weather research.

A century ago, colonial meteorologists had little knowledge of global mechanisms, and even if that knowledge had existed, they had no means of measuring, observing, or predicting their behavior. Forecasts had to rely on statistical correlations—empirical observations that certain events in distant regions of the world were often followed months later by corresponding events in other regions. For example, the Indian weathermen predicted monsoon rainfall from things as disparate as barometer readings in South America, South Africa, and Zanzibar; rainfall in Southern Rhodesia and Indonesia; snow accumulations in the Himalayas; and water temperatures in Dutch harbors.

Following in that tradition, Indian weather forecasters now produce predictions that are considerably better than random guesswork. But they long missed out on the great revolution that swept through Western meteorology in the late forties and early fifties, a revolution based on the use of computers and mathematical models that are grounded in the fundamental physics of fluid motion. John von Neumann, often regarded



Changes in tropical east-west atmospheric flow, sometimes called Walker circulation, account not only for El Niño and the Southern Oscillation but presumably for monsoon variations as well. As long as the circulation moves clockwise (top), it sweeps warm surface water westward, causing the thermocline, or boundary between warm surface waters and underlying cool layers, to be shallow off Scuth America. The upward movement of warm, moist air produces heavy rainfall in the Western Pacific. But during El Niño (bottom), the flow reverses and warm water flows eastward, suppressing the nutritious upwelling, driving fish away and producing heavy rain over the Latin American Coast. STI researchers are exploring how such changes are related to changes in monsoon rainfall half a year before and after, and thousands of miles to the West.

as the father of the modern electronic computer, originally designed that machine with weather forecasting in mind. In 1949, he and meteorologist Jule Charney wrote a famous paper that spelled out the basic weather-modeling principles. In this approach, observations on wind, temperature, and pressure are collected around the world and are converted into a uniform grid of numerical data. These are fed into the model, which then calculates step by step how individual parcels of air will be heated, moistened, convected, and swept along to generate weather.

Over the years, a number of young Indian meteorologists came to the United States to learn the art of numerical weather prediction. Through STI, India is reaping returns from these expatriates. Among them is T. N. Krishnamurti at Florida State University, who arrived in the United States in 1962 and now coordinates United States research under STI's Monsoon Program I. Krish is often credited with being the first to emphasize the importance of tropical events in forecasting weather, even in temperate climes. He has authored some of the best computer models for short- and medium-term monsoon forecasting.

Several Indian participants have been visiting Krishnamurti's lab in Tallahassee to modify models for use in India. One, A.K. Bohra of the India Meteorological Department in Delhi, recently carried a version of Krish's regional model to India, where it will be tested for operational short-term forecasting. At this time, however, India has no computer large and fast enough to capitalize on a medium-range (five- to seven-day) forecasting model, but the United States and Indian governments are working on an agreement under which India would acquire an advanced supercomputer. Meanwhile, Indian scientists are testing simplified versions of global models on a non-operational basis.

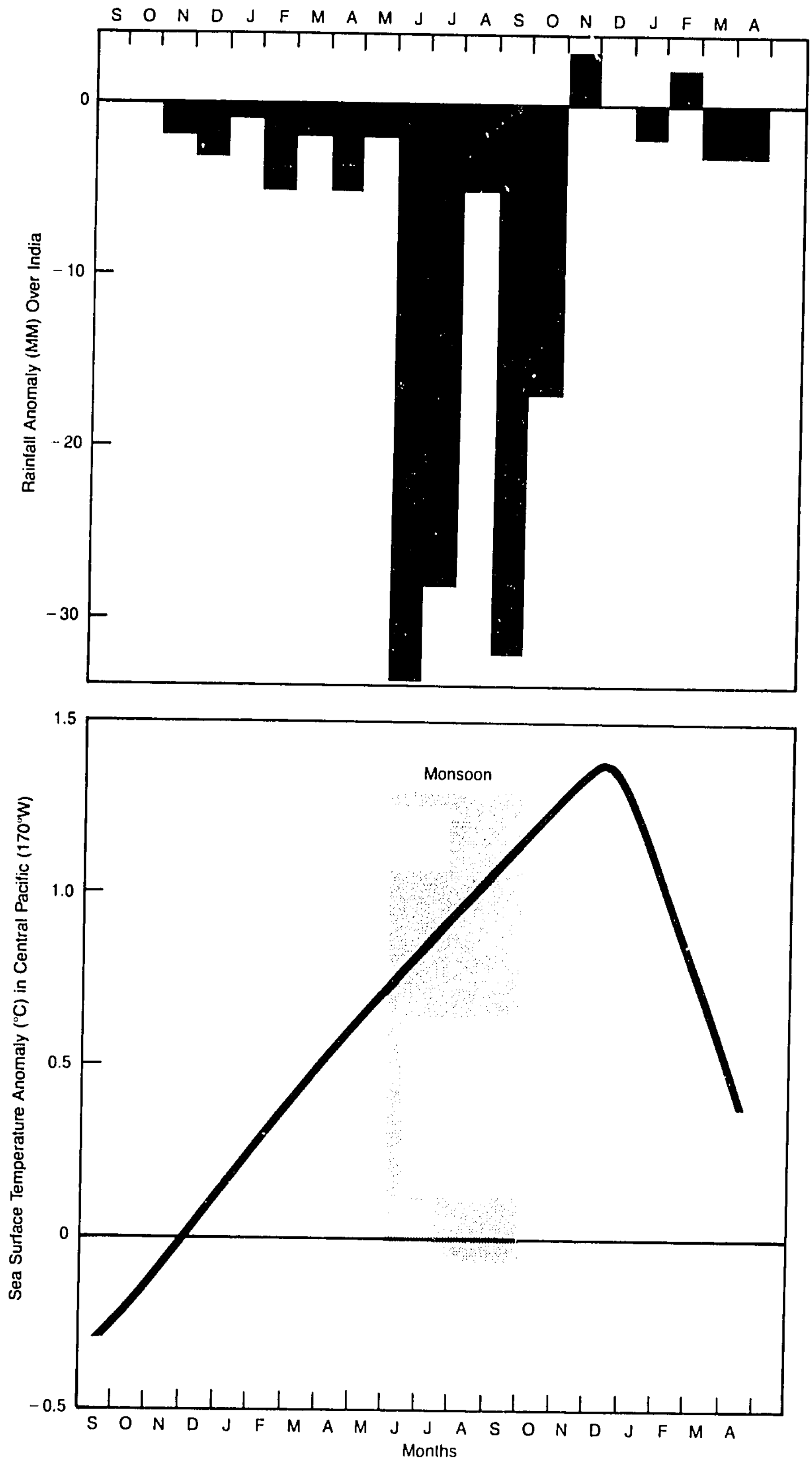
Currently, the most promising advances in longer-range weather forecasting combine the Western modeling approach with important discoveries first identified in India's statistical tradition. One such discovery, the Southern Oscillation, has

A century ago colonial meteorologists predicted monsoon rainfall from barometer readings in Zanzibar, snow accumulations in the Himalayas, and water temperatures in Dutch harbors.

emerged from a scientific curiosity to become one of the hottest topics in meteorology today. First noticed by several 19th century meteorologists, it was best described by Sir Gilbert Walker, a Cambridge University mathematician posted to India in 1904 as Director General of the India Meteorological Department. Walker specialized in finding correlations between atmospheric pressure changes from very distant parts of the world.

Walker defined the Southern Oscillation in the following terms: "When pressure is high in the Pacific Ocean, it tends to be low in the Indian Ocean from Africa to Australia. These conditions are associated with low temperatures in both these areas, and rainfall varies in the opposite direction to pressure." In essence, he discerned a see-saw relationship connecting the eastern Pacific with the western-Pacific Indian Ocean region. He deduced that the see-saw's movement during winter and spring was a pretty reliable indicator of monsoon rainfall in the following summer.

Outside of India, the see-saw's significance remained obscure until the late 1960s, when the Norwegian-born scientist, Jacob Bjerknes of UCLA, connected it with another meteorological curiosity, El Niño events in the eastern Pacific. Named by 18th century Peruvian fishermen for the Christ Child, El Niño is a peculiar Christmastime warming of sea surface water, spelling the end of the fishing season off Latin America's Pacific coast. When that warming occurs, the normal upwelling of cold, nutrient-rich sea-bottom water in which fish thrive is suppressed. Though this happens each December to some extent, scientists now reserve the term El Niño for the really severe episodes that occur every three to seven years with far-flung consequences. A 1973-74 El Niño wiped out the catch of Peruvian and



Researchers have discovered an interesting correlation between poor monsoon rains and El Niño. Comparing the amount of rainfall over India during the three El Niño years of 1957, 1969, and 1972 (upper graph) with the average sea-surface temperature in the central Pacific during the same years (bottom graph), they find an intriguing pattern. (Zero on the horizontal axis represents normal sea temperatures and rainfall.) Monsoon rains that normally fall from June to September are well below normal, while the temperature of the sea surface, slightly above normal in January, rises steadily until it reaches its peak in December—the onset of El Niño. Meteorologists are keeping a careful watch on sea surface temperatures and monsoon rains to help them predict El Niño six or seven months ahead of its arrival. Someday, El Niño may help them predict poor monsoons.

United States anchovies, which are widely used as livestock feed, helping to drive up corn and meat prices around the world.

Often the direct threats to human life are even more severe and far-reaching. The 1982-83 El Niño triggered storms that inundated parts of Peru and Ecuador under 11 feet of rain, rearranged beaches in California, and brought cold-waves that exhausted heating-oil supplies in the eastern United States. Parts of Australia, Africa, Indonesia, and Malaysia withered under droughts so severe that in Australia, for example, entire towns were consumed in fire-storms. And, as Walker himself would have predicted, six months later, the Indian monsoon failed.

The association of these events was dramatic confirmation of the teleconnection Bjerknes proposed between El Niño and the Southern Oscillation. This El-Niño-Southern-Oscillation syndrome is now so firmly rooted in meteorologists' lore that they commonly shorten it to the acronym ENSO. The favored explanation for ENSO consists of an ocean-atmosphere interaction. The atmospheric component is called Walker circulation in Sir Gilbert's honor, and its influence may be as important and far-reaching as Hadley circulation. While Hadley's is basically north-south and Walker's is east-west, some believe the two are intimately coupled. In combination, they dominate weather in the tropics and greatly influence it elsewhere.

In general outlines, the Walker circulation appears to be initiated by the east-to-west trade winds initially kicked up by Hadley circulation. These sweep the warm surface waters of the equatorial Pacific and Indian Oceans westward, literally piling up water to the point that sea-levels in the western Pacific stand 15 to 20 inches higher than in the eastern Pacific off Latin America. This causes upwelling of cold, nutrient-rich waters essential to Latin American fisheries and also creates a hot spot in the western oceans that helps energize monsoons. The ocean temperature differences also drive deep convection in the atmospheric Walker circulation that helps sustain the process. The ocean-spanning cells thus formed are called Walker cells. Recent research suggests

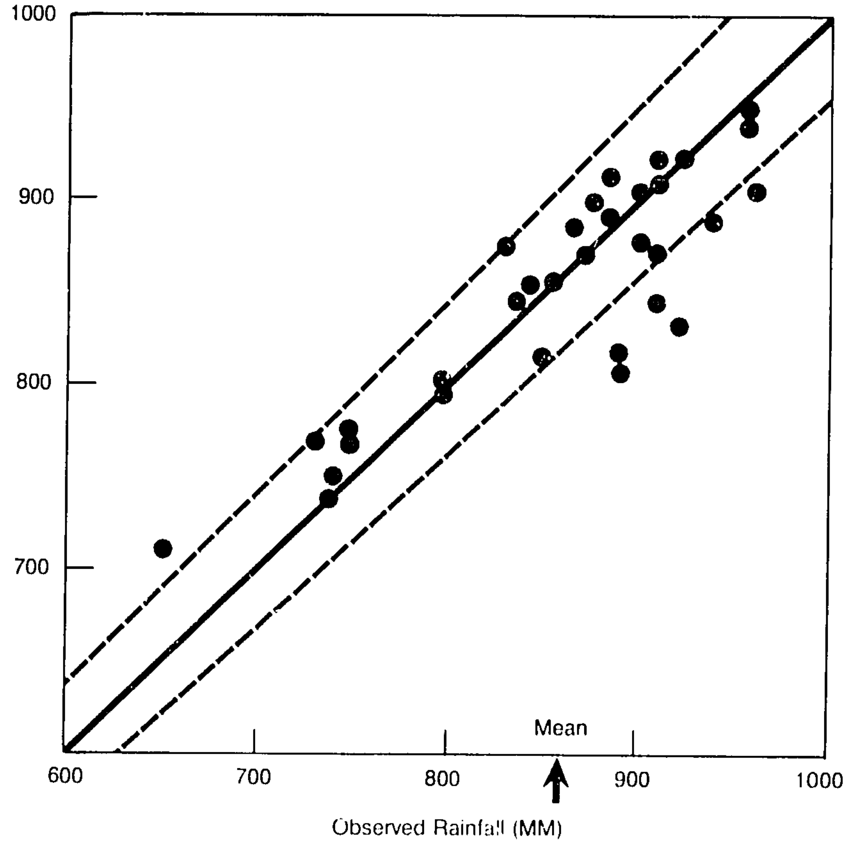
The 1982-83 El Niño triggered storms that inundated parts of Peru and Ecuador, rearranged beaches in California, and brought cold waves to the eastern United States.

that tropical heat sources create wave patterns that propagate northeastward across the Pacific to affect weather at higher latitudes. This is of enormous interest to North American forecasters.

Likely causes of monsoon failures, meteorologists suspect, are events that either cool the western hot spots or shift them eastward. If, for example, the normal state of the Southern Oscillation—with low pressure in the western Pacific and high pressure in the eastern Pacific—flips, the trade winds either falter or reverse direction. The western hot spot, then, may simply spread eastward toward the Peruvian coast, creating El Niño. All this appears to cause major shifts in world weather patterns, including the monsoon.

As with many meteorological phenomena, the ENSO-monsoon chain of events seems to be circular: while El Niño is a good predictor of feeble monsoon rainfall the following summer, the level of monsoon rainfall is also a fair predictor of the state of the Southern Oscillation the following winter. Meteorologists hope some day to predict monsoons, El Niños, and other weather events two or more years before their occurrence.

One of the chief authorities on long-range monsoon modeling is another of those Indian expatriates, J. Shukla of the University of Maryland, scientific leader and coordinator for the United States Program II research. In the early Seventies, as a young fledgling meteorologist, Shukla mustered enough nerve to deliver a paper at a conference in Tokyo criticizing some of the ideas of the late Jule Charney, the eminent American pioneer of meteorological theory and computerized forecasts. Present at the meeting, Charney asked his young critic a few questions, then invited him to his hotel room to continue the discussion. Subsequently, Shukla wound up at MIT doing



Among the tantalizing fruits of STI monsoon research is a single equation that predicts average rainfall for the whole of India during a single monsoon season. It employs only two simple parameters—the location of a high-pressure ridge over the Indian subcontinent during April and the general upward or downward trend in barometric pressure in Darwin, Australia during the spring preceding the monsoon. The equation was formulated by J. Shukla and D. A. Mooley at the University of Maryland. The graph above summarizes how the equation would have performed over 32 years: Each dot represents a prediction for one year. The slanting solid line indicates where the dots would have been had the prediction been perfect; the dotted lines represent errors of plus and minus five percent. The graph shows that forecast errors of more than five percent occurred in only seven years.

graduate and post-doctoral work under Charney's guidance, and since then the two have often collaborated in research and writing.

Shukla makes the paradoxical-seeming argument that long-range monsoon forecasts of monthly and seasonal averages may be fundamentally easier than short-range prediction of daily weather. A basic problem with all computer forecasting is that models necessarily oversimplify the complex real interactions between land, sea, and atmosphere, while the actual atmospheric observations are skimpy and often erroneous. The longer computer simulations are run, the greater the problem. "Run long enough, models tend to predict ridiculous things," says Shukla. "One of the breakthroughs in the business was learning how to simply ignore these systematic errors without doing violence to the model as a whole."

Shukla, for example, proposed the concept of "boundary forcing," suggesting that long-range monsoon forecasters can ignore much of the fine-scale variability of temperature, pressure, and winds with which short-range forecasters are concerned, especially those in temperate climates. Instead, long-range forecasters can employ a comparatively small number of large-scale, slowly-changing, easy-to-measure properties such as average sea-surface temperatures in the Pacific and Indian Oceans, soil moisture on the Indian sub-continent, and snow cover over Eurasia and in the Himalayan mountain range. While the resulting forecasts have little that's reliable to say about day-to-day weather at any specific location, they often have valuable things to say about, say, the average rainfall over the Indian subcontinent through a given monsoon season. Such predictions are particularly valuable to planners trying to manage food and water supplies and also, no doubt, to other long-range weather forecasters working thousands of miles away.

Among the first research results to emerge so far from Monsoon Program II is a simple equation Shukla and an Indian colleague, D. A. Mooley, have derived to predict the total rainfall in India for a given monsoon season. The prediction is based on only two easily-measured parameters—the trend of the ENSO barometric pressure see-saw between April and January as measured in Darwin, Australia, and the location of a high-pressure ridge over India in April. Using historical readings of these two parameters from 1939 to 1984, Shukla and Mooley find their equation could have predicted the following season's rainfall with no more than a seven percent error.

Would-be weather modelers in both the United States and India have lately begun paying more attention to something that Indians working in the old statistical tradition noticed long ago: that the intensity of monsoon rainfall and the breaks between rains seem to follow patterns. They are particularly intrigued by evidence that rainfall intensity during the monsoon seems to behave as though it has periodicities of about 10 to 20 days and about 30 to 50 days, with averages of 15 and 40 days respectively. Evidence of these two patterns has been found elsewhere in the tropics. In recent years, for example, satellites have revealed patterns of parallel cloud bands that seem to recur over the same regions at roughly 15- and 40-day intervals moving generally northwards during the monsoon season.

What these cycles represent is a matter of considerable dispute. Some, like monsoon specialist Peter Webster at Pennsylvania State University, believe they occur because falling rain cools the underlying earth and halts the rain-generating convection, so the center of convection and rainfall shifts northward to an adjacent warm area. Webster believes that it takes 10 to 20 days for the earth to heat to the convective point again, accounting for the average 15-day cycle. Others think it is not so much the cooling and warming cycle that is important as a wetting and drying cycle. (Rising humid air tends to reinforce convection once it starts, since as the humidity condenses into rain, still more heat is released to the surrounding air.)

Still others, including R. N. Keshavamurthy and his colleague V. Satyan at

Shukla makes the paradoxical-seeming argument that long-range monsoon forecasts of monthly and seasonal averages may be fundamentally easier than short-range.

the Physical Research Laboratory in Ahmadabad, believe that both the 15- and 40-day cycles reflect wave- or eddy-motions perturbing the monsoon winds as they flow past the tip of India. These eddies grow by spawning convection, which in turn feeds on heat released by condensing moisture. In this view, the explanation for the average 40-day period is that the wavelike influences simply take 30 to 50 days to travel around the world back to their starting point. In fact, some meteorologists claim to be finding evidence of this 40-day cycle affecting not only rainfall but also pressure, temperature, and wind in places far distant from India.

Whatever the explanation, the existence of weather cycles would have obvious implications for forecasting, especially if it were possible to discover the various influences that make these cycles vary in length. In fact, a whole new generation of computer models, called spectral models, has been emerging in recent years based on the concept of weather as a complex product of many interacting, globe-spanning wave patterns.

For all the exciting discoveries that STI researchers and others have been making about global mechanisms, the connections are not simple, even though they are often obvious. Sometimes, for example, a given ENSO state seems to occasion floods in California and at other times droughts. The challenge now is to uncover the hidden linkages that transform these apparent contradictions into obvious outcomes.

Tom Alexander is a freelance writer based in Washington, D.C.

SOLID STATE SCIENCE AND ENGINEERING

In remote villages that have no other source of power, solar energy often provides lighting and refrigeration for medicines. In this village of 4,000 inhabitants 35 miles outside New Delhi, a solar panel provides power to pump drinking water from the community well. Villagers proudly demonstrate their pump to a visiting American team led by S. K. Deb from the Solar Energy Research Institute.

Solar Power and Microorganic Miners

Amorphous silicon may make solar cells competitive with fossil fuels, while innovative mining methods go to work on low-grade ores.

by Jane Alexander

From its first application as an exotic power source for spacecraft in the early 1960s, photovoltaics has often tantalized the energy community with its magical ability to make electricity from the sun's rays with no noise or moving parts. By now a $200 million industry has emerged, producing solar cells to power calculators, watches, radio transmitters and repeaters, and navigation aids, plus such things as irrigation pumps, desalination plants, educational television, and refrigeration for medicines in remote villages. Even a few experimental utility power stations have been built. But if photovoltaics is to fulfill its promise of competing with conventional large power stations, it will have to become a lot cheaper.

A. D. Krantz, who coordinates the STI photovoltaics program for the United States Department of Energy, says, "The cost of photovoltaic panels has dropped from hundreds of dollars per peak watt 15 years ago to $6.00 a peak watt today. But to make photovoltaics competitive with fossil fuels and nuclear power, the cost will have to drop to $1.00 or less."

Krantz says that such things as automated production and large orders can help reduce costs, but to get the rest of the way you need better technology.

That technology may already be here in the form of amorphous silicon, a kind of silicon in which the molecules are randomly arranged instead of being rigidly aligned as in the crystals that have been used for most photovoltaic applications until now. Conventional solar cells are made on wafers sawed from cylinders or cast blocks of highly purified crystalline silicon, an inherently expensive technology that requires a lot of hand labor. Amorphous silicon cells, by contrast, can be mass produced on large sheets of glass, plastic or steel by the vacuum deposition process requiring much less materials and labor. The process is more suited to mass production. And because these deposits can be very thin, less than a micron or a millionth of a meter thick, less of the costly material is needed. "The low-cost pot at the end of the rainbow lies in the use of truly thin-film photovoltaic cells," says former DOE scientist J. Richard Burke.

In calculating solar-cell economics, there's a trade-off between cost and efficiency, efficiency being the measure of how much of the solar energy that falls on the cell actually gets converted into electricity. The lower the efficiency, the greater the area of cells required to produce a given amount of electricity. So going hand in hand with the pursuit of lower costs is the pursuit of greater efficiency.

Early commercial amorphous silicon cells were only about four or five percent efficient but have been improving rapidly. Devices now exist in the laboratory with efficiency of more than 12 percent, comparable to the best commercial cells made of crystalline silicon, which approach 14 percent. The main drawback of amorphous silicon technology, however, is degradation: most amorphous cells lose efficiency after exposure to sunlight, whereas crystalline cells do not. "If we could make reliable solar cells with as much as eight percent efficiency and reduce the cost to below $1.00, we could revolutionize the world," says Krantz. Already there is a large market for amorphous silicon—about $50

With the solar panel in place over the well, a villager prepares to pump.

million in consumer products like calculators and watches," says Krantz.

One promising approach toward increasing efficiency of the silicon is the multijunction cell. By combining layers of different amorphous silicon alloys, each tailored to respond to a specific part of the light spectrum, it may be possible to make cells with efficiencies of 15 to 20 percent.

The essence of the STI project is to gather new fundamental knowledge about amorphous silicon, to probe the very heart of matter with the goal of improving efficiency and lowering the cost of photovoltaic cells. Krantz emphasizes the basic nature of the research. Using such exotic measurement techniques as laser Raman spectroscopy, positron annihilation, and Mossbauer studies, Indian and American researchers are exploring the optical, electrical, and structural properties of suitable alloys, such as silicon and germanium and silicon and carbon. Later, they will investigate better methods of depositing gaseous silicon on substrate wafers and other ways of improving the manufacturing process.

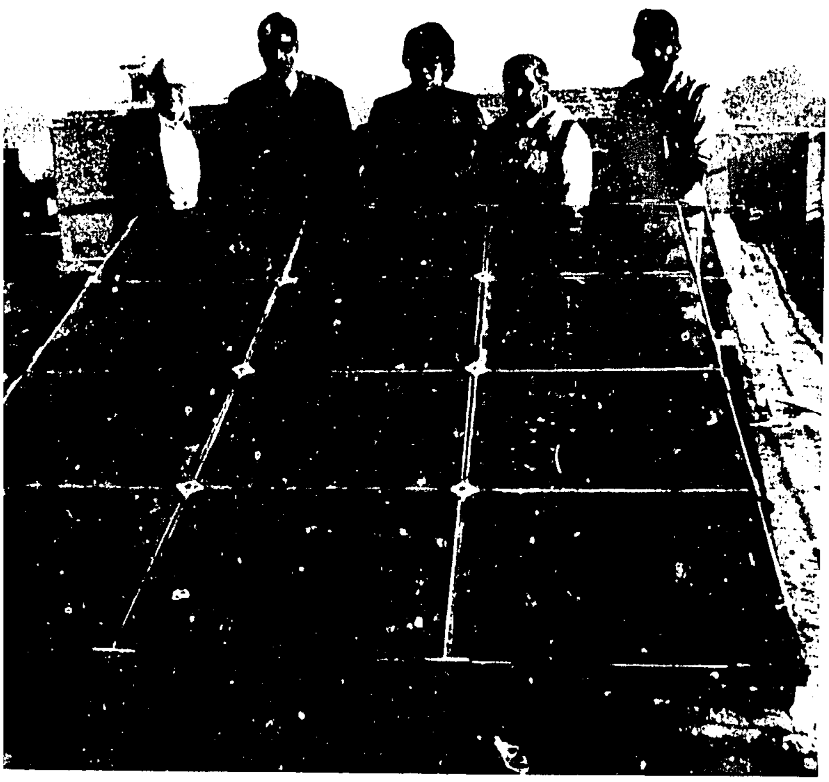
A major drawback of amorphous silicon is the mysterious Staebler-Wronski effect, the light-induced degradation responsible for efficiency losses. For reasons no one fully understands, the sun's rays cause amorphous silicon thin films to lose as much as 20 percent efficiency in the first year of use. STI researchers are trying to obtain not only a theoretical understanding of the effect but also a way of circumventing it. If successful, it will make a significant impact on the world's energy future.

The mineral engineering portion of the solid state science program, which is managed by Ranga Komanduri at the National Science Foundation, is a wide-ranging investigation of many problems that now afflict the mining industry. Beset by low and fluctuating mineral prices, rising production costs, stricter pollution regulation, declining non-ferrous ore reserves and grades, the mineral industry is seeking cheaper ways of extracting strategic metals from low-grade ores and recovering byproducts from mine tailings.

A better approach to these problems of extraction and purification, many believe, is to borrow a trick from nature and put bacteria to work.

"Bacterial leaching is an age-old phenomenon," says Tapan Mukherjee of the United States National Science Foundation. "Where water collects, bacteria do their work. We have vast low-grade reserves of copper, zinc, and lead in this country in the form of sulfide ores." But environmental concerns have necessitated the installation of scrubbers to eliminate acid-rain producing sulfur dioxide." Since bacteria don't produce that noxious gas, it makes sense to augment their natural leaching process.

"In the United States nearly 30 percent of our copper is already produced by bacterial leaching," says Mukherjee. "But bugs are fragile. They multiply slowly. The



Mounted on the rooftop of the village headman, this solar panel made of crystalline silicon provides street lighting for about four hours a day and powers the radio and television for the community center. From left to right, J. Pankove, SERI; Mitra, Department of Non-conventional Energy, India; R. Tsu, SERI; the village chief; and a technician.

Bacteria do their work cleanly and elegantly. Some get the energy they need by oxidizing the sulfur in metal sulfides, releasing water-soluble sulfates of iron, copper, and uranium.

problem is to find out at the microbiological level what microbes are doing, how they feed and reproduce. Then we can help them along."

A related problem has to do with getting the most from low grade ores where non-ferrous resources are poor and the percentage of metal in ore is low. From one ton of rock you get two to four pounds of copper, for example. The mountains of slag from most mines still contain valuable copper, but mines are small and isolated. The most efficient and economical way of mining the remaining copper is to dig ditches around the slag heaps, sprinkle water in the ditches, and let bacteria grow naturally.

Bacteria do their work cleanly and elegantly. Members of the thiobacillus family, for example, get the energy they need by oxidizing the sulfur in metal sulfides, releasing the metal as water-soluble sulfates of iron, copper, and uranium. These bacteria also excrete sulfuric acid, which aids in separating the metal from the ore body. In addition, when thiobacilli oxidize iron, they turn it into a form that can oxidize other ores. "It's a neat little cycle," says David Holmes of General Electric's Corporate Research and Development Center in Schenectady, New York. "Here's a bacteria that has its cake and eats it."

But bacteria work slowly. So one of the STI projects aims to speed up the rate at which *Thiobacillus ferrooxidans*, one of the most common organisms in the leaching process, extracts metal from ore. In the past decade, G. Agate in the Department of Microbiology at Maharastra Association for the Cultivation of Science Research Institute in Pune and his colleagues have amassed a good collection of these little organisms, and they are studying such characteristics as the way various strains grow, metabolize, and reproduce.

Holmes will collaborate with Agate in the selection and breeding of the bacteria with the goal of improving the rate, extent, and range of their leaching capabilities. Holmes is using recombinant DNA techniques to investigate the unusual biochemistry of these interesting little organisms. He wants to find out which of the improved laboratory strains will be tough enough to survive in competition with naturally occurring microorganisms in concrete leaching ponds. He is looking at ways to genetically engineer superior strains. Many bacteria can be poisoned by toxic metals or water temperatures that are too low or too high, for example.

A second project strives to develop the appropriate computer software to find the most efficient and cheapest ways of crushing, grinding, and floating minerals in order to separate them from their ores.

"The knowledge we have gained as to when and how to carry out each operation in the mining process has developed gradually, empirically, over the centuries," says Mukherjee. "Playing these steps by ear means many of them are inefficient and costly. Now, however we're beginning to analyze the entire mineral processing circuit with computer modeling."

Many large mills process as much as 100,000 tons of ore a day, and handling that amount of material requires careful controls at every step of the mining process, according to S. Chander at Pennsylvania State University. The quality of the ore may change from day to day or over the life period of the mine, and it is important to know how those changes will affect the end product. Computer modeling can describe exactly what's going on in each stage of the circuit and then advise when to add more or less reagent (a chemical that aids in the separation process), speed up or slow down the grinding or crushing operation, or change the amount of ore that is fed to the mill, for example.

STI researchers are also trying to develop a computer model of coal-flotation, an important step in cleaning coal. Most of India's coal deposits contain lots of impurities, such as ash, that can't be removed by simple washing techniques, and the United States faces stringent environmental requirements for removing sulfur from coal. So both countries can benefit from the most efficient and cheapest methods of removing impurities.

Fine coal is cleaned by mixing it with water to form a slurry, then blowing air through banks of flotation cells, vessels containing agitators. With the help of reagents, clean coal levitates to the top, and the waste material is withdrawn from the bottom of the cell. Depending on the kind of coal, differing amounts or kinds of reagents and varying amounts of water or air are needed. Computer modeling will aid in designing the most efficient circuit configurations and optimum operating conditions for a particular quality of coal.

The last project focuses on developing new and better reagents to separate minerals from a variety of low grade and complex ores.

While the solid state science and engineering program got a late start, researchers are already hard at work and highly enthusiastic about their wide-ranging projects.

Jane Alexander is a freelance writer living in Washington, D.C.

APPENDICES

Indo-U.S. Science and Technology Initiative Project Activities

HEALTH PROGRAM

I. BLINDNESS RESEARCH

Project Area & Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
CATARACT RESEARCH		
A Case-control Study of Senile Cataract	Dr. R. Sperduto, Co-PI, Dr. R. Milton, Dr. B. Underwood, National Eye Institute (NEI) Dr. V. Reddy, Oakland University Dr. S. Varma, University of Maryland Dr. S. Srivastava University of Texas	Dr. M. Mohan, Co-PI, Dr. K. Ramachandran, Dr. S. K. Angra, Dr. A. K. Prabhakar, Dr. N. Jaffery, and Dr. R. L. Mathur Rajendra Prasad Centre, All India Institute of Medical Sciences (AIIMS), New Delhi
NUTRITIONAL BLINDNESS		
Anterior Segment Collagenase Activity in Keratomalacia	Dr. B. Underwood, NEI Dr. D. Newsome, Johns Hopkins University (through 1985) Dr. R. Thoft, Harvard Medical School	Dr. V. Reddy, Dr. R. Reddy, and Dr. Raghuramulu, National Institute of Nutrition (NIN), Hyderabad
Absorption of Vitamin A in Diarrhea Treated with and Without Oral Rehydration Solution	Dr. B. Underwood, Co-PI, NEI	Dr. V. Reddy, Co-PI, NIN Dr. N. Raghuramulu, NIN
Use of Monoclonal Antibodies for Early Detection of Vitamin A Deficiencies	Dr. R. Thoft, Harvard Medical School	
EALES' DISEASE		
Laboratory and Clinical Studies of Eales'Disease	Dr. C. Schepens, Harvard University, Dr. C. Kupfer, NEI, Co-PI Dr. R. Nussenblatt, NEI Dr. S. Meyers, NEI Dr. K. Mittal, Madurai University Histocompatibility Testing Branch, National Institutes of Health (NIH) Dr. R. Auerbach University of Wisconsin	Dr. V.R. Muthukkaruppan, PI, Madurai University Dr. R. M. Pitchappa, Madurai University Dr. P. Namperumalsamy, Madurai University

II. INFECTIOUS DISEASES

Project Area and Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
MALARIA		
Detection of Infected Mosquitoes Using Two-site Immunoradiometric Assay	Dr. R. Nussenzweig, New York University Medical Center Dr. F. Zavala, New York University School of Medicine Dr. R. Gwadz, National Institute of Allergy and Infectious Diseases (NIAID)	Dr. V.P. Sharma, Malaria Research Centre (MRC), Delhi Dr. S.K. Subbarao, MRC Dr. D.S. Choudhury, MRC
Studies on Transmission Blocking Immunity in *Plasmodium cynomolgi* and *P. knowlesi*	Dr. R. Carter, NIAID Dr. L. Miller, NIAID	Dr. Nitya Anand, CDRI (through 1985) Dr. D.C. Kaushal, Central Drug Research Institute (CDRI)
Studies on Antigenic Variation During Relapses of *Plasmodium cynomolgi* Infections	Dr. R. Nussenzweig, Dr. A. Cochrone, New York University Dr. T. McCutchan, NIAID	Dr. Nitya Anand, CDRI Dr. D.C. Kaushal, CDRI Dr. G.P. Dutta, CDRI Dr. Pawan Sharma, CDRI
Immunization of Simians with Purified Malarial Antigens	Dr. L. Miller, NIAID Dr. R. Nussenzweig, New York University	Dr. Nitya Anand, CDRI Dr. V.P. Sharma, MRC Dr. G.P. Dutta, CDRI Dr. Siki Puri, CDRI
LEPROSY/TUBERCULOSIS		
Production, Characterization and Supply of Monoclonal Antibodies to *M. leprae*	Dr. T. Buchanan, Dr. S.R. Khanolkar, Dr. R.A. Miller, and Dr. D. B. Young, University of Washington, Seattle	Dr. Indira Nath, AIIMS Dr. P.R. Mahadevan, Foundation for Medical Research, Bombay Dr. K.V. Desikan, Central JALMA Institute for Leprosy, Agra
Comparison of FLA-ABS Tests using *Mycobacterium leprae* and ELISA Test for Antibody to Phenolic Glycolipid, for Detection of Subclinical Infection in Leprosy	Dr. T. Buchanan, University of Washington	Dr. K.V. Desikan, Central JALMA Institute of Leprosy
Development of *M. leprae*—Specific Human R Cell Clones	Dr. D.J. Volkman, NIAID, Dr. A. Fauci, NIAID, (through 1985) Dr. J. Aubrus, NIAID	Dr. Indira Nath, AIIMS
Demonstration and Characterization of Specific Glycolipid in Infected Human Tissues and Human Derived *Mycobacterium leprae.*	Dr. P.J. Brennan, Colorado State University	Dr. P.R. Mahadevan, The Foundation for Medical Research, Bombay
Studies of Macrophage Metabolism and Function after *M. leprae* Infection as an Indication of Host Parasite Interaction	Dr. Z.A. Cohn, Rockefeller University	Dr. P.R. Mahadevan, Foundation for Medical Research Dr. Indira Nath, AIIMS
Role of Dendritic Cells in Antigen Induced *in vitro* Lymphoproliferative Responses in Leprosy	Dr. Z.A. Cohn, Rockefeller University	Dr. Indira Nath, AIIMS

Project Area and Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
Evaluation of Biological Significance of Phenolic Glycolipid Antigen Derived from *M. leprae*	Dr. P. Brennan, Colorado State University Dr. T. Buchanan, University of Washington	Dr. Indira Nath, AIIMS
Development, Validation and Application of Immunodiagnostic Techniques for Diagnosis of Clinical Tuberculosis	Dr. R.S. Yalow, Solomon Berson Research Lab., Bronx, New York Dr. E. Straus, State University of New York Dr. B.R. Bloom, Albert Einstein College of Medicine, Bronx, New York	Dr. N. Kochupillai, AIIMS
FILARIASIS		
Immunodiagnosis and Immunopathogenesis in *Bancroftian* Filariasis	Dr. E. Ottesen, NIAID Dr. R.G. Crystal, National Heart, Lung and Blood Institute, NHLBI, NIH	Dr. S.P. Tripathy, Tuberculosis Research Center, Madras
Antigen, Antibody and Immune-complex Profiles as Applied to Immunodiagnosis of Human Filariasis	Dr. R.A. Hamilton, John Hopkins University (through 1985)	Dr. B.C. Harinath, Mahatma Gandhi Institute of Medical Science, Sevegram
Immune Response Dynamics in Filariasis; Characterization of Immunosuppression; Evaluation of Antibody-mediated Killing of *Wucheria bancrofti* Infective Larvae	Dr. G.I. Higashi, University of Michigan	Dr. Santhanam, and Dr. M.V.V.L. Narasimham, Communicable Diseases, Delhi and Rajahmundy
Detection of Circulating Parasite Antigens as Clinical and Epidemiological Tool for Filariasis	Dr. G.J. Weil, Washington University, St. Louis	Dr. Santhanam, National Institute of Communicable Diseases, Delhi and Rajahmundy

III. REPRODUCTIVE PHYSIOLOGY

Project Area and Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
IMMUNOLOGICAL CONTRACEPTION AND THE TREATMENT OF INFERTILITY		
Development of Anti-LHRH Vaccine for Male Fertility Regulation	Dr. C.W. Bardin, The Population Council	Dr. G.P. Talwar, National Institute of Immunology, (NII), Delhi
Immunization with Zona Pellucida Antigens	Dr. B.S. Dunbar, Baylor College	Dr. S. Sehgal, Post-Graduate Research Institute Dr. G.P. Talwar, NII
Active Immunization with Ovine FSH as a Means of Male Fertility Regulation	Dr. H.G. Raj, Louisiana State University	Dr. N.R. Moudgal, Indian Institute of Science (ISS)

Project Activities

AGRICULTURAL PROGRAM

I. BIOLOGICAL NITROGEN FIXATION RESEARCH

Project Area & Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
MOLECULAR GENETICS		
Rhizobia & Azotobacter	Dr. Donald Helinski, University of California, San Diego	Dr. H.K. Das, J. Nehru University, Delhi
Rhizobium	Dr. Frederick Ausubel, Massachusetts General Hospital, Boston, Mass.	Dr. Sushil Kumar, Indian Agricultural Research Institute (IARI), New Delhi
Symbiosis	Dr. David Kuykendall, U.S. Department of Agriculture (USDA) Beltsville, Maryland	Dr. Sushil Kumar, IARI, New Delhi
Blue-Green Algae	Dr. Robert Hazelkorn, University of Chicago	Dr. J. Thomas, Bhabha Atomic Research Center (BARC)
RHIZOBIA-LEGUME SYMBIOSIS		
Soil Inoculation to Improve Crop Production	Dr. Ben Bohlool, University of Hawaii	Dr. N.S. Subbarao, IARI, Delhi
Symbionts	Dr. Donald R. Keister, USDA, Beltsville, Maryland	Dr. Y.D. Gaur, IARI Dr. S.V. Hegde, University of Agricultural Sciences, Bangalore
Synergism between Mycorrhiza and Rhizobia	Dr. James Trappe, Oregon State University Dr. G. Bethlenfalvay, Western Regional Research Center, USDA, Albany, California	Dr. K.V.B.R. Tilak, IARI, New Delhi Dr. D.J. Bagyaraj, University of Agricultural Sciences, Bangalore
AZOLLA AND BLUE-GREEN ALGAE		
Photosynthesis	Dr. Marvin Lamborg, Battelle-Kettering Research Lab.	Dr. G.S. Venkataraman, IARI, Delhi
Sporulation	Dr. Gerald A. Peters, Battelle Dr. D. William Rains, University of California, Davis	Dr. S. Kannaiyan, Tamil Nadu Agricultural University (TNAU) Dr. P.K. Singh, Central Rice Research Insitute
Phosphorus Efficiency	Dr. D. William Rains, University of California, Davis	Dr. S.K. Goyal, IARI
Blue-Green Algae	Dr. William Evans, Battelle	Dr. S. Shanmugasundaram, Madurai University Dr. S. Kannaiyan, TNAU

II. NITROGEN USE EFFICIENCY RESEARCH

Project Area & Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
PADDY RICE (FLOODED SOILS)		
Quantification	Dr. Duane S. Mikkelsen, F.E. Broadbent University of California, Davis	Dr. N.N. Goswami, IARI
Physicochemical	Dr. William Patrick, Jr., Louisiana State University	Dr. M.C. Sarkar, IARI Dr. S.K. Mohanty, Central Rice Research Institute Dr. T.S. Manickam, Tamil Nadu Agricultural University, Coimbatore Dr. C.S. Khind, Punjab Agricultural University (PAU), Ludhiana
UPLAND (WELL-DRAINED) SOILS		
Crop Management	Dr. James Power, USDA Lincoln, Nebraska	Dr. N.N. Goswami, IARI
Ammonia Volitization	Dr. Richard Fox, Pennsylvania State University	Dr. Rajendra Prasad, IARI
Labelled N	Dr. Lynn Porter, USDA Fort Collins, Colorado	Dr. O.P. Meelu, PAU
Blocking	Dr. John M. Duxbury, Cornell University	Dr. M. C. Sarkar, IARI

III. BIOMASS FUELWOOD PRODUCTION RESEARCH

Project Area & Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
SPECIES SELECTION, TESTING AND IMPROVEMENT	Dr. F.T. Ledig, Institute of Forest Genetics Berkeley, California Dr. J.R. Goodin, Texas Tech University Lubbock, Texas Dr. R.F. Stettler, University of Washington	Dr. A.N. Chaturvedi, National Botanical Research Institute (NBRI), Lucknow
CULTURAL SYSTEMS FOR SHORT ROTATION FORESTRY AND AGRO-FORESTRY	Dr. David Dawson, Rhinelander, Wisconsin Dr. R.F. Stettler, University of Washington Dr. C. Davey, North Carolina State University Dr. Edward A. Hanson, U.S. Forest Service	Dr. P.V. Sane National Botanical Research Institute, Lucknow Dr. A.N. Chaturvedi, NBRI
APPLICATION OF TISSUE CULTURE AS A BIOTECHNOLOGICAL TOOL IN THE EFFICIENT PROPAGATION OF WOODY SPECIES	Dr. J.R. Goodin, Texas Tech University Lubbock, Texas Dr. Stanley L. Krugman, USDA Forest Service Washington, DC	Dr. A. Mascarenhas, National Chemical Lab, Pune Dr. P.V. Sane, NBRI

Project Activities

MONSOON RESEARCH: NUMERICAL WEATHER PREDICTION OF MONSOONS

I. DEVELOPMENT OF NUMERICAL MODELS

Project Area & Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
Development of a Regional Model	Dr. M.B. Mathur, National Meteorological Center	Dr. S.S. Singh, Indian Institute of Tropical Meteorology
Role of Initialization Schemes on Monsoon Prediction	Dr. A. Kasahara, Dr. R. Errico, National Center for Atmospheric Research	Dr. U.C. Mohanty, Indian Institute of Technology-Delhi
Development of a Global Spectral Model for Medium Range Prediction	Dr. D. Williamson, National Center for Atmospheric Research	Dr. V. Satyan, Physical Research Laboratory
Monsoon Prediction Using Quasi-Langragian Regional Model	Dr. M.B. Mathur, National Meteorological Center	Dr. V. Satyan, Physical Research Laboratory
Limited Area NWP Model for Short Range Prediction	Dr. T.N. Krishnamurti, Florida State University; Dr. M.B. Mathur, National Meteorological Center	Dr. M.C. Sinha, Dr. A.K. Bohra, India Meteorological Department
Development of Global Spectral Model for Medium Range Forecasts	Dr. E. Schneider, University of Maryland	Dr. B.K. Basu, India Meteorological Department
Development of Numerical Analysis Schemes	Dr. R. McPherson, National Meteorological Center	Mr. K. Prasad, Mr. R.K. Bansal, India Meterological Department

II. DEVELOPMENT OF SYSTEMS FOR ACQUISITION AND PROCESSING OF INITIAL DATA

Project Area and Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
Optimum Interpolation Method for Objective Analysis	Dr. R. McPherson, National Meteorological Center	Dr. S. Rajamani, Indian Institute of Tropical Meteorology
International Radiosonde Comparison Project	Mr. F. Finger, National Meteorological Center	Mr. N. Seshadri, India Meteorological Department
Improvement in Data Reception and Data Quality	Dr. A. Thomas, National Meteorological Center	Mr. T.K. Ray, Mr. V. Dayal, Mr. J.U. Hingorani, India Meteorological Department

III. SATELLITE DATA PROCESSING AND ARCHIVING

Project Area and Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
Moisture Profile Retrievals from Polar Orbiting Satellites	Dr. C. Hayden, NOAA/NESDIS	Mr. D.G.K. Murty, Space Applications Centre
Precipitation Estimation from INSAT	Dr. D. Martin, University of Wisconsin	Mr. B.M. Rao, Space Applications Centre
Derivation of Vertical Temperature Soundings from Polar Orbiting Satellites	Dr. C. Hayden, Dr. H. Woolf, NOAA/NESDIS	Mr. P.N. Khanna, India Meteorological Department

IV. RESEARCH ON BASIC MONSOON DYNAMICS

Project Area and Title	*U.S. Senior Scientists*	*Indian Senior Scientists*
Sensitivity of Limited Area Model Forecasts to Initial Data and Boundary Conditions	Dr. F. Carr, University of Oklahoma	Mr. B.M. Chhabra, India Meteorological Department
Convection on Cumulus and Meso-scales	Dr. T.N. Krishnamurti, Florida State University Dr. R. Johnson, Colorado State	Dr. G. Mohan, Indian Institute of Technology-Kanpur
Simple Model Studies of Linear Response to Diabatic Heating	Dr. A. Vernekar, University of Maryland	Dr. M. Sankar Rao, Indian Institute of Science-Bangalore

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