The classic image of India that most people can conjure has cows, beggars, small children and sari-clad women all jostling for space on crowded streets. That image still reflects reality — but with palpable differences. Along some of those streets now are gleaming, modern buildings where men and women churn out medicines for poor countries. Many children are being immunized with affordable vaccines produced by India’s own biotechnology industry. And if the country continues to prosper as it has for the past decade, there soon may not be many beggars left.

Since 1991, when India discarded its socialist past and instituted broad reforms, its economy has been growing rapidly. By 2032, India’s economy could be larger than those of all but the United States and China, according to an estimate by the investment banking firm Goldman Sachs.

In the following pages, we look at what effect these changes have had on India’s life sciences. Indian biotechnology companies have been remarkably successful, but they have made most of their money copying patented drugs. To sustain growth, they will have to become more innovative. The same is true of basic-research institutes, which have only recently begun to be globally competitive.

While developed nations are seeing their populations shrink, half of India’s growing population is under the age of 25. The government must improve India’s ailing universities to educate and train these young people and stem the haemorrhage of its brightest students to the United States and Europe. It must also untangle the still-rampant red tape that stifles creativity and set up ethics panels to monitor clinical research.

Most important, it must find a way to protect its people from grave health crises. India has among the highest rates of HIV/AIDS, diabetes and tuberculosis, which threaten to sap the country’s resources and derail its progress.

This is a critical juncture for India. The opportunities, whether in partnership with multinational pharmaceutical companies or as an outsourcing centre for clinical trials, are many. Seized judiciously, they can allow India to build a scientific and technological future to be proud of.

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Then and now

Inder Verma celebrates the recent success of India’s biotechnology industry, applauds the increased investment and looks to the future.

“Your job is to collect urine in the men’s bathroom and bring it to the laboratory at the end of the day.” These were the instructions my thesis adviser gave me when I began my graduate career in 1966. Others would then purify factors from the urine that might function as a male contraceptive in monkeys. He pointed to a 20-litre glass bottle with a broken rim and a small glass funnel. I was expected to obey his orders — and I did. (My only intellectual contribution was to switch to a larger funnel, which made it easier for both the donors and for me.)

A few months later I was told that monkeys were no longer available and the study was being shelved. From now on I would work with a plant researcher in another lab. At no point was I consulted during these arrangements. I was merely a graduate student expected to do as my supervisor commanded. In the years since, the situation has improved, and the overbearing attitude of many advisers is becoming a thing of the past. Young scientists in India are more independent and increasingly resentful of the autocratic system.

For many decades, Indian universities have churned out biologists, many of whom move to the United States or Europe. Those that remain in India are usually destined to publish in local or low-impact scientific journals. Life-science research in India has been constrained by insufficient funds and equipment coupled with a lack of will to compete with the rest of the world. Funding agencies such as the Council of Scientific and Industrial Research have always emphasized translational research but, because the success of such programmes rests on a strong foundation of basic science, the results were often dismal. Indian medical schools, lacking resources for research, have failed to train scientists in translational research. Not surprisingly, India has not produced a single original drug sold in the world market. All this, I hope, is about to change.

I’ve been to India every year for the past 35 years, have visited many institutions, met many colleagues, students and young investigators and participated in countless meetings. In that time, I’ve witnessed the growth of Indian biosciences with concern and pride. Recently, I’ve been delighted by a run of excellent papers published in top-tier journals by scientists in India. And I’ve been impressed by the desire of the biotech and pharmaceutical industry to undertake novel challenges.

The first prime minister of India, Jawaharlal Nehru, believed that science is the way out of poverty. The scientific opportunities in India may well prove him to be a true visionary, but there is much work to be done first.

**Novel ideas**

Biotechnology companies are among the most profitable in the country. Today, Indian companies provide 22% of the world’s generic drugs — copies of brand-name drugs. India also manufactures a significant proportion of vaccines made for the developing world.
Within India, vaccines against hepatitis B are manufactured by Indian companies and sold for less than 30 cents per dose. True, most of India's biotech and pharmaceutical industry is based on duplicating existing products, but that still requires considerable sophistication and know-how. But with the passage of a new law on 23 March this year forbidding companies from making copycat drugs (see page 480), Indian companies will be forced to be more innovative.

But how do we encourage such innovation? In the mid-1980s, the Indian government established the Department of Biotechnology (DBT) and invited several researchers—including me—to serve on its overseas advisory committee. We encouraged the DBT to furnish state-of-the-art laboratories, provide increased funds for research, reduce the bureaucracy required for importing research materials such as restriction enzymes, initiate projects that promote the sharing of expensive equipment, offer visiting fellowships and build manpower to support the biotech industry.

Since the DBT's inception, its budget has grown from a meagre US$15 million to more than US$125 million a year. That may not be much compared with the US$27 billion budget of the US National Institutes of Health, but it's a good start.

**Increased investment**

In addition to the DBT, there are at least three major funding sources for life scientists within India, so finding funds for a good project is no longer a hurdle. Indian scientists have been able to win significant funding from international sources such as the US National Institutes of Health, the Bill & Melinda Gates Foundation, the European Union and the Wellcome Trust (see page 489).

Despite this, India will not succeed unless it encourages innovation and rewards excellence. Most Indian universities still operate under a feudal system, which stifles creativity. Science is best carried out in an irreverent environment, where the status quo is challenged, often at the risk of offending superiors. But the Indian scientific enterprise frowns on questioning authority and rewards obedience. Senior scientists are too often selected by seniority and rank, rather than their ability and achievements.

In common with many scientists at institutes in neighbouring China, Indian researchers once hired are there to stay. I do not know of any case in which someone was denied tenure or did not have their contract renewed because of low productivity. This problem is compounded by the lack of lateral mobility in India. Most scientists who train abroad return to India for family reasons and are loath to live away from their home town. They would sooner go back abroad than swap cities or states within India.

But science thrives when there is a nucleus of scientists striving for excellence. The Indian Institute of Science in Bangalore and the National Institute of Immunology in New Delhi have achieved this. Scientists at these institutes, which are independent of universities, are publishing in international journals and are being invited to prestigious national and international meetings. To be competitive on a global scale, India needs to nurture such centres rather than worry about equitable distribution of the country's resources.

These centres can also encourage collaborations across cities and disciplines. Modern biology requires the expertise of scientists from many different fields. Unfortunately, scientific departments at Indian institutions and universities have traditionally operated as islands. Experts in microbiology, biophysics and biochemistry might all work within a few feet of each other and yet hardly interact, much less collaborate. The government should provide incentives for interdisciplinary research. It should also encourage academics to forge alliances with industry, market their inventions and set up technology-transfer offices.

Government officials are always coming up with catchy slogans, such as 'IT today, BT tomorrow,' but often they do not follow through on those ambitious plans. India is still far behind the United States, Europe and Japan. Although India has the advantage that its citizens know English, it still lags behind other Asian countries such as China and South Korea.

India sometimes gives the impression that it will never compete properly in the global arena. But life scientists will be able to if they can learn from the success of the IT sector.

India's position in the global IT industry is a source of pride and confidence. Graduates of the Indian Institutes of Technology (IIT) have started numerous companies worldwide, and their innovative spirit should inspire biologists to be more adventurous.

Last year, 60 Minutes, a popular investigative television programme in the United States, featured the IITs. When the interviewer asked N. R. Narayana Murthy, founder and chairman of the multibillion-dollar company Infosys, what his son would do if he did not pass the arduous entrance examination for the IITs, Murthy replied, without skipping a beat: "Well, we have back-ups like Cornell, MIT and Stanford."

I don't usually support starting new institutions, but an Indian Institute of Integrative Biology, much like the successful IITs, is worth considering. Alternatively, the IITs could broaden their curriculum to include degrees in biology and biotechnology.

**Promoting science**

The time is ripe for life sciences to blossom in India. Every day, newspapers carry headlines reporting Indian successes in information technology, tales of rich Indian biotech tycoons and highlighting the enormous purchasing power of the growing middle class. In my experience, the Indian government, regardless of which party was in power, has always been highly supportive of science. But the current left-leaning administration is particularly so (see graphic, above). For example, the government recently gave the Indian Institute of Science a one-off grant of about US$25.3 million. Prime minister Manmohan Singh has also endorsed the creation of a US$250-million independent agency to support basic research.

India is not a poor country — indeed, it is rich in natural and intellectual resources — but it has many poor people. More than 700 million people, nearly 70% of the population, live in rural areas but contribute only 20% of the GDP. Until this disparity changes, vast sectors of the Indian population will never see the benefits of biotechnology or modern medicine. It's very clear what India needs to do to become a world player in the life sciences, but unless the government, researchers and the industry work together to put the solutions into practice, all their best laid plans will not succeed.

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Biotech boom

India’s thriving biotechnology industry is threatened by a change in the law. Will the current high levels of investment be enough to secure its future? K. S. Jayaraman finds out.

Every year, on the presumed birthday of Krishna, the blue-skinned Hindu god, New Delhi’s Mathura Road is choked with traffic. Buses, cars and bullock carts packed with devotees advance toward Vrindavan, where Krishna is believed to have been born 5,000 years ago.

This August, pilgrims to Krishna’s legendary birthplace will pass an imposing three-story structure of sandstone and glass. Inside, at The Centre for Genomic Applications (appropriately shortened to TCGA, the letters of the genetic alphabet), white-coated scientists are devoted to a god of a different kind. On the centre’s first birthday in May 2005, scientists acquired a new Hewlett-Packard supercomputer, the fastest in India, worth a whopping US$2.2 million. Capable of four trillion operations a second, the computer places the centre among the ranks of international institutions such as the Wellcome Trust Sanger Institute in Britain and the Institute for Molecular Science in Japan.

TCGA is the youngest of several biotechnology laboratories that have sprung up in India in recent years. It is a shared venture between the Chatterjee Group, a Kolkata-based industrial house, and two government agencies — the Council of Scientific and Industrial Research (CSIR) and the Department of Science and Technology — that shared the US$ 5.7 million cost of construction.

The centre, which aims to provide world-class facilities for genomics and proteomics, is the first to be built by a public–private partnership. It also symbolizes the current revolution in India’s biotechnology industry.

With fewer than 300 registered companies, the biotechnology sector is small but is gaining in global stature. According to the World Health Organization, India is the fourth largest producer of pharmaceuticals, and 66.7% of its exports go to developing countries. For example, the Pune-based Serum Institute of India, once a small manufacturer of tetanus toxin, now makes 80% of the world’s measles and DTP (diphtheria, tetanus and pertussis) vaccines (see ‘A shot of success’, opposite).

Other companies that have made a global impact include the Mumbai-based company Cipla, which rewrote the rules of the international AIDS drug market when, in 2001, it introduced inexpensive generic antiretroviral drugs. Strand Genomics in Bangalore has formed a partnership with Japan’s MediBIC to develop informatics solutions for pharmaceutical companies in Japan. And Avesthagen, also based in Bangalore, has joined up with France’s bioMérieux to develop diagnostic instruments for medical and industrial applications.

Profits soar

In 2003–04, Indian biotechnology companies together had a revenue of more than US$700 million (see graphic, below). This year, they have surpassed US$1 billion. “The biotech-
A SHOT OF SUCCESS

On a sunny Friday morning in January, the students of the Shiva Shivan School in Hyderabad were ushered, one by one, into a room where a doctor and nurse stood with syringes.

The school’s 470 students, ranging in age from 5 to 12 years, all received a shot of Shanvac-B, a hepatitis B vaccine produced by a local company, Shantha Biotechnics. At just Rs18 per dose (equivalent to US 40 cents), the vaccine is so affordable that scenes like this are commonplace.

Such widespread vaccinations were unthinkable early in 1997 when GlaxoSmithKline (GSK) sold its product at Rs500 per dose. But later that year, Shantha’s hepatitis B vaccine became India’s first recombinant product to be made indigenously in the healthcare sector. Today this vaccine is available in 52 countries and makes up 40% of UNICEF’s supply.

Varaprasad Reddy says he launched the company, named after his mother Shantha, after he heard multinational companies disparage India’s dependence on them for its vaccine needs. “India can position itself as an affordable base for producing vaccines for the entire developing world,” he says.

Shantha’s success inspired four other Indian companies to bring out their own hepatitis B vaccine. As a result, GSK’s share of the vaccine in the Indian market has plummeted to 10% from a virtual monopoly (see graph, below). The Serum Institute, based in Pune, is the world’s largest manufacturer of the diphtheria, tetanus and pertussis vaccine, which now protects three out of ten of the world’s children, according to figures released by UNICEF. The Mumbai-based Haffkine Institute supplies 75% of India’s oral polio vaccine, and Indian Immunologicals in Hyderabad, already the world’s largest manufacturer of vaccines for foot-and-mouth disease, plans to make human vaccines against rabies, hepatitis B and measles.

“Not many people are aware that the United States is one of the largest importers of measles vaccine from India,” says Nirmal Kumar Ganguly, director-general of the Indian Council of Medical Research. “But Indian companies are only beginning to venture into original territory.”

“IT is true we have not made any new vaccine on our own,” says Krishna Ella, managing director of Bharat Biotech.

To encourage innovation the Department of Biotechnology is supporting the development of 11 original vaccines. Four of these, for rotavirus, cholera, Japanese encephalitis and malaria, will enter clinical trials this year.

Outside of India, the number of companies producing vaccines has dwindled to 4 in 2005 from 26 in 1967. This reduction presents an opportunity for India and other developing countries, says Ganguly.

The Global Alliance for Vaccine and Immunization, launched by the Bill & Melinda Gates Foundation in 2000 is purchasing vaccines from Indian companies at low prices. In return, these companies are assured a long-term contract to guarantee revenue. The alliance has awarded contracts to the Serum Institute, Shantha Biotechnics and Panacea Biotec to make and test heat-stable vaccines.

K. S. Jayaraman

World class: researchers from the Institute of Bioinformatics in Bangalore managed to characterize the human X chromosome.

A biotechnology sector is witnessing an impressive 40% annual growth,” says Kiran Mazumdar Shaw, chief executive of Biocon, Bangalore. “The profile of Indian biotech companies is undergoing a change and they are becoming international.” Biocon, the most profitable biotechnology company in India, this year posted revenues of US$150 million, a 30% increase over the previous year.

Shaw, sometimes called India’s ‘biotech queen’, and several other company chiefs are quickly becoming household names in India. Five of them won this year’s Padma awards, the nation’s highest honour for civilians. “Never in the history of these coveted awards has a small section of the industry grabbed the entire limelight,” says N. Suresh, editor of BioSpectrum magazine, published in Bangalore.

The biggest boost to the biotechnology industry has come from the government itself. “Biotech is the government’s priority area,” says science minister Kapil Sibal. Less than a year after Sibal took office, the Department of Biotechnology (DBT) released an ambitious plan to create a biotechnology industry that would generate US$5 billion in revenues per year and create one million jobs by 2010.

As part of its strategy, the DBT is planning to make it easier for foreign-owned companies to set up in India. Foreign investors have in the past had to knock on the doors of several different government agencies. But the DBT’s new plan is to set up a single independent authority to replace the committees at different ministries.

The DBT has also subsidized the construction of three biotechnology parks, including Genome Valley (see ‘Land for rent’, overleaf) and aims to help finance at least ten such parks by 2010. Together with the Ministry of Information Technology, the DBT plans to build the country’s first biotech/IT park. This

NATIVE COMPANIES DOMINATE INDIA’S PHARMACEUTICALS MARKET

SOURCE: THE WTO AND INDIA’S PHARMACEUTICAL INDUSTRY
“Welcome to Genome Valley”. The giant green-and-white sign stretches across the road on the way from the Hyderabad airport to this bustling south Indian city. But don’t blame the taxi driver if he meets your queries with a blank look — almost no one knows where the valley is.

Not too long ago, Hyderabad was dubbed ‘Cyberabad’, reflecting its strength in information technology. These days, it’s aiming for pastures new: the biotechnology sector. For now though, the ‘genome valley’ exists only in the minds of those who conceived it eight years ago.

The name refers to a 600-square-km area bound by an imaginary line that links nearly every institution in the city that has anything even remotely to do with science.

“I actually suggested that the whole of Hyderabad should be declared Genome Valley,” says Bhim Sen Bajaj, chairman of the southern chapter of the All India Biotech Association. “They did not listen to me.”

In reality, Genome Valley is the Knowledge Park, 40 km from the city on 80 hectares of government land and set up by ICICI, a premier financial institution. There is no public transport to the area and, at one point, cars have to snake through muddy roads, occasionally interrupted by cows and hens.

The park offers modern modular laboratory units of approximately 300 square metres to rent. In the past six years, 13 companies have rented spaces, and an additional 7 have booked space.

A second area of the valley is the Biotech Park, which is intended for companies to use for manufacturing units. This park, which opened in 2001, has an impressive arched entrance to its 126 hectares — but it is almost empty. Officials say 19 companies have purchased plots and 7 have begun construction, but the promised infrastructure for these companies is not yet in place. The water pipe was laid only a few months ago.

To make matters worse, builders are selling the land at about US$112,000 per hectare, nearly ten times the government’s original price.

“I had no choice,” says S. P. Vasireddi, chairman and managing director of Vimta Labs, who is building a US$10-million facility in a 4.5-hectare plot. “Land of this size is not available inside the city.”

For the moment, the valley has one undisputed king: Bharat Biotech, built by US-educated microbiologist Krishna Ella and his wife Suchitra. “Whenever a government guest wants to visit the genome valley, he or she is brought to our company,” says Seema Kumar, general manager of public relations for the company.

Bharat Biotech, which earned US$10 million in 2004, produces vaccines, but the most used product at the company’s headquarters may not be one that it manufactures itself. Instead it’s the anti-snake venom stocked in the first-aid kit. “The place is crawling with snakes,” says the company’s communication manager U. V. L. Ananda.

To help employees with the three-hour daily commute, Bharat Biotech operates shuttle buses to the city. In the meantime, there is no hospital, bank or police station nearby. ICICI bank is noted for its cash machines, but it has yet to set one up in its own Knowledge Park.

Bharat Biotech buys water from private tankers and generates its own electricity to operate its vaccine unit because the unit in nearby Turkapally village crashes at the slightest environmental disturbance, such as rain or lightning. The company has gleaming state-of-the-art technology, but no broadband Internet connectivity and, until recently, workers there could not use their mobile phones. Says one employee: “We do cutting edge science in such a primitive setting.”

K. S. Jayaraman
is expected to attract bioinformatics contracts from around the world and foster innovative companies. "We not only want to build on the existing platform but expand the base to create global leadership in biotechnology," says Maharaj K. Bhan, secretary of the DBT. "This will require larger investments."

The science ministry has already announced a 50% increase in its budget over the past year for drug-discovery research and called for proposals from the industry.

To encourage small businesses, the DBT gives out grants of Rs5 million (US$115,000) for proof-of-concept research and low-interest loans for subsequent product development and commercialization. Any money that companies spend on maintaining patents is also exempt from income tax.

Patent crackdown

One reason for this increased investment is that from 1 January 2005, a new patent law, which brings India in line with World Trade Organization (WTO) rules, came into effect. Indian companies will have to honour international patents and stop producing unlicensed generic drugs, a major source of their revenue over the past 30 years (see graphic, above).

The pharmaceutical industry’s research and development spending has shot up from Rs2 billion in 2000 to Rs8 billion in 2004, says D. G. Shah, secretary-general of the Indian Pharmaceutical Alliance. Chennai-based Orchid, which earned US$82 million in 2004, is building a US$15-million plant. Biocon is adding a US$170-million research lab and manufacturing plant to its assets in Bangalore. And Wockhardt, a large pharmaceutical company, last year built a US$50-million complex — India’s largest — in Aurangabad. Nicholas Piramal India, which opened its US$25-million research facility in September 2004, says it already has eight original products, including potential treatments for cancer and diabetes, in preclinical tests. Other generic producers such as Dr Reddy’s Laboratories in Hyderabad and Delhi-based Ranbaxy Laboratories are moving along this innovation route even as they continue to scout for patent-expired generics in the US market.

Still, "the odds are not in India’s favour in the innovation driven global drug markets", says Prasanta Ghosh, a consultant to Cadila Pharmaceuticals in Ahmedabad and former adviser to the DBT. "We are nowhere compared with China, South Korea, Cuba or Brazil," he says. "Our research has not gone into product development."

Local companies will also have to compete on Indian soil with powerful multinational companies, others warn. Companies such as Merck and Bristol-Myers Squibb left India years ago because cheap copycat drugs cut into their profits. But with the WTO rules enforced to protect their patents, those companies will return, says Yusuf Hamied, Cipla’s chairman. “Multinationals will invade India in force and wipe us out in five years,” he warns.

Companies face other obstacles too. “Biology is extremely technology-driven and yet we do not make any instruments in this country,” says Syed Hasnain, director of the Centre for DNA Fingerprinting and Diagnostics in Hyderabad. “Except for flasks and syringes, every instrument is imported. We do not trust the local centrifuges, so we import even these.” Most institutes also have limited access to fundamental research. India’s role in basic research is not available.

When the Bangalore-based Institute of Bioinformatics (IOB) needs someone who knows the computer programming language Oracle, it can find a good candidate within a week. That’s because there are so many good programmers in the Industrial Technology Park, where the institute is based.

Akhilesh Pandey, a professor at the Johns Hopkins University, founded the IOB in 2002. In three years, it has published more than 40 papers, including several in high-impact journals. In April 2005, the IOB published its annotation of the X chromosome (H. C. Harsha et al. Nature Genet. 37, 331–332; 2005). The study, carried out in direct competition with Britain’s Wellcome Sanger Institute, marks the first time that any institute other than a genome-sequencing centre has characterized an entire human chromosome.

Training biotechnologists

With a booming biotechnology business and a demonstrated prowess in information technology, there should be a dozen such bioinformatics success stories in India. But even the big Indian pharmaceutical companies have been slow to adopt bioinformatics.

Although the country grants nearly 300,000 degrees and diplomas in biotechnology, bioinformatics and the biological sciences each year, companies struggle to find skilled staff. "Most of them get their degrees without seeing a biotech lab," says Krishna Ella, managing director of Bharat Biotech International in Hyderabad. Most of those qualified also leave for greener pastures; up to 90% of those who finish their PhDs at the Indian Institute of Science go abroad. India needs to find ways to stem that massive brain drain, says Ella.

In the meantime, companies are wooing scientists to India from around the globe. According to estimates from the Indian Pharmaceutical Alliance, 10% of the new recruits at senior levels are expatriate Indians or foreigners.

Geetha Vani Rayasam, an IISc graduate, joined the Ranbaxy Research Labs in November 2004 after spending several years in Europe and the United States. Rayasam says many more like her would return to India if a few essential things were fixed. “There are several things that need to be improved, like a more professional approach, less bureaucracy and providing better salaries,” she says. “But the day is not far off when India might be leading the way in drug discovery.”

K. S. Jayaraman is Nature’s India correspondent.
Vaccines on trial

One of the largest ever vaccine studies is under way in Kolkata. Paroma Basu uncovers the benefits, and difficulties, of inoculating 60,000 people against cholera and typhoid fever.

Famed for its poets and filmmakers, disgruntled Marxists and sleepy government clerks, Kolkata, a city of about 14 million people in northeastern India, may seem an unlikely setting for one of the largest clinical trials in the world. In the poorest areas of this city, residents live in homes jammed together along winding sewage-littered pathways and rely on shared toilets and drinking water. Typhoid fever and cholera are endemic in India, and are chronic problems in Kolkata. Cholera, in particular, has a tenacious grip on the state of West Bengal, often called the ‘homeland of cholera.’

The vaccine industry has been reluctant to commit resources to the development of vaccines for some of the world’s poorest people. But a grant of US$40 million from the Bill & Melinda Gates Foundation is helping to introduce affordable vaccines to cities such as Kolkata. The money has funded the five-year Diseases of the Most Impoverished (DOMI) Programme, an initiative of the South Korea-based International Vaccine Institute (IVI).

DOMI is studying the social, economic and clinical effects of introducing vaccines into six other countries: Pakistan, Bangladesh, China, Indonesia, Vietnam and Thailand. Since 2000, it has launched two cholera studies, six projects investigating typhoid fever and another six exploring shigellosis, a common bacterial disease.

The work is unprecedented, says John Clemens, the IVI’s director, not only because of the project’s size but also because it focuses on a demographic long ignored by drug companies, lawmakers and public-health officials.

In a unique research effort, 60,000 Kolkata slum-dwellers will participate this summer in one of the largest clinical trials in the world. Live in homes jammed together along winding sewage-littered pathways and rely on shared toilets and drinking water. Typhoid fever and cholera are endemic in India, and are chronic problems in Kolkata. Cholera, in particular, has a tenacious grip on the state of West Bengal, often called the ‘homeland of cholera.’

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In a unique research effort, 60,000 Kolkata slum-dwellers will participate this summer in phase III trials of an oral cholera vaccine. Last November, researchers injected the same population with a vaccine against typhoid fever. The typhoid fever vaccine was developed at the US National Institutes of Health, and was donated by GlaxoSmithKline. The cholera vaccine is modelled on a widely available oral vaccine, Dukoral, which was developed in Sweden during the 1970s.

But at several dollars a dose, Dukoral is too expensive for most developing countries. Vietnamese scientists licensed the technology in the early 1990s and formulated a cheaper version at about 20 cents per dose. With the IVI and Kolkata-based National Institute of Cholera and Enteric Diseases (NICED), Shantha Biotechnics, an Indian biotechnology company, is developing a local version of the Vietnamese vaccine and has procured regulatory clearances for the Kolkata trials. It has also secured the right to market the vaccine if it is approved, says Raman Rao, head of clinical research for Shantha.

Meanwhile, the roadblocks encountered during these trials in Kolkata are an example of the difficulties of carrying out such a programme, from political and religious tensions and bureaucratic delays to mistruths spreading like wildfire among the largely illiterate trial participants.

The project got off to a smooth start in 2002, with Kolkata epidemiologists performing a year-long surveillance study before identifying two slums that were particularly hard-hit by cholera and typhoid fever. But the next step was a bureaucratic nightmare, says Dipika Sur, deputy director of epidemiology at the NICED. The institute had to get an endless list of clearances from, among others, the national health ministry committee, local councillors, ethics and human rights groups, Hindu priests, Muslim imams and community thugs.

But the clearances were easy compared with gaining the confidence of the study participants. During the typhoid vaccine trials, for instance, rumours spread that scientists were injecting cancer cells into people. Others believed they were being sterilized. “There was mass panic,” Sur recalls.

About 65% of the targeted study group eventually gave their informed consent and received the typhoid jab. Sur thinks a big reason for this level of success was her tactic of employing 250 slum-dwellers to serve as the ‘face’ of the study, working as community health workers, field supervisors and sample collectors.

The strategy paid off largely because of staggeringly high unemployment levels in the slums. Montu Chandra Das, who was previously unemployed, now earns roughly US$60 per month as a health worker. “It feels good to help others,” he says.

Das goes door-to-door sending patients with persistent symptoms of diarrhoea or fever to one of seven ‘health outposts,’ where patients receive free blood tests and medicines if diagnosed with cholera or typhoid.

“I like the way that the health workers come to check on us all the time,” says Kamala Das, a 35-year old domestic helper who is taking part in the study. “Now we can see a doctor and be treated right away,” adds another study member, Gopal Balmiki, a car driver who shares a room with 11 family members. “We know now that it’s really important to keep the bathroom clean and drink unpolluted water.”

Paroma Basu is a freelance writer based in Madison, Wisconsin.
India's drug tests

Drug companies are converging on India to conduct low-cost clinical trials. But is it ready to become the outsourcing centre for the world? T. V. Padma investigates.

The average cost of a clinical trial in the United States is US$180 million. The average cost in India is US$100 million. No surprise, then, that multinational companies are flocking to India to launch their trials. “It’s a lot cheaper to do things in India,” says Sameer Deb, general manager of government affairs at GlaxoSmithKline’s office in Mumbai.

Multinational companies are not the only ones to benefit financially from these studies — India does too. The consultancy firm McKinsey estimates that US and European pharmaceutical companies will spend US$1.5 billion per year on clinical trials in India by 2010.

India has several advantages as a host for such trials. Its biggest asset is probably the size of its population at more than 1 billion. In addition, Indians are increasingly suffering from the same illnesses as Americans and Europeans — diseases for which companies are desperate to find cures. For instance, at least 70 million Indians suffer from heart disease and 35 million have diabetes. It also has the edge over most developing countries because of its sophisticated hospitals and because many of its medical personnel speak English.

But India does not have the robust infrastructure needed to sustain this expansion. It does not even have a central database listing all the trials currently under way, despite each one having to be cleared by the Drug Controller General of India.

In addition, contract research organizations (CROs) are struggling to recruit enough participants to its trials, despite India’s enormous population. An even greater obstacle is the lack of trained staff. Trials of this size will need an estimated 3,000 investigators, 600 medical institutions and 9,000 other professionals — numbers India cannot produce at present.

Some CROs, in partnership with educational institutes and trial sponsors, are addressing this by setting up specialized institutes and centres of clinical excellence.

The bureaucracy-ridden Indian system is no small barrier, either. Officially, the government has limited the time it takes to accredit trials to 90 days for phase I, 45 days for phase II and 45 days for phase III trials. But “we are yet to see such speedy approvals in reality”, notes Dhananjay Bakhle, director of regulatory affairs at Aventis Pharma, based in Mumbai.

The thorniest issue by far may be the ethics of conducting these trials. In one instance, scientists at Johns Hopkins University in Baltimore, Maryland, and the Regional Cancer Centre in Thiruvananthapuram, India, tested two experimental anticancer molecules on 27 oral cancer patients from 1999 to 2000 (see Nature 412, 466; 2001). But the researchers tested the drugs without the required federal or university approvals and without adequate preliminary tests in animals (see Nature 414, 835; 2001).

Following this incident, the Indian government ordered a full review of the ethics and safety of all trials. In 2000, the Indian Council of Medical Research (ICMR), the country’s premier agency for biomedical research, issued guidelines for research on humans. The following year, the health ministry released its policy on good clinical practice.

But scandals continued to surface. In 2003, private clinics across India used a generic version of the anticancer drug letrozole to treat more than 435 women with fertility problems. This trial did not have clearance from the health ministry, and the women involved did not know that the drug was not approved for this use. The manufacturer, Mumbai-based Sun Pharmaceuticals, denies ordering this trial.

Government agencies concede that the regulations need to be tightened. “We are looking into strengthening institutional ethics committees and are conducting training workshops for them,” says Vasantha Muthuswamy, deputy director-general of the ICMR.

Tightening the regulations will protect the trial participants, but it may be possible to go further. “Participants should benefit from any drugs that result from the trials,” says Prasanta Ghosh, president of the biotechnology division of Cadila Pharmaceuticals, based in Ahmedabad. In which case, expansion of clinical trials in India could benefit everyone.

T. V. Padma is a freelance writer based in New Delhi.
Ayurveda

Science and business are racing to tap the 3,000-year-old system of medicine for new drugs, says T. V. Padma.

In November 1987, ethnobotanist Palpu Pushpangadan was trekking through the tropical forests in the southern Indian state of Kerala. Pushpangadan and his colleague were struggling to keep up, but their guides, men from the local Kani tribe, kept popping brownish-black fruit about the size of a cardamom pod into their mouths, and walking briskly ahead. Curious, the scientists ate the fruit and felt a surge of energy.

Locally known as arogyapacha, meaning ‘evergreen health’, the fruit, Trichopus zeylanicus, is noted in ancient Indian texts as a source of health and vigour. With the tribe’s help, Pushpangadan and his colleagues studied the plant extracts, isolated the active ingredients and developed an energy-boosting drug, Jeevani, combining T. zeylanicus with two other herbs mentioned in the texts.

The team patented the drug and granted a manufacturing licence to the Indian company Arya Vaidya Pharmacy. Sales now garner nearly US$230,000 a year. Under an agreement signed in 1995, the Kani got a 50% share of the US$30,000 licence fee, and have earned nearly US$50,000 a year in royalties.

The Jeevani story is one often told in India as a success both in scientifically validating traditional knowledge and in setting up a model that benefits the local population.

Updating traditional remedies

Today, several laboratories and private companies are racing to tap the ancient Indian system of medicine, Ayurveda, for new drugs. The government’s Council of Scientific and Industrial Research (CSIR) and the health ministry are jointly digitizing Ayurvedic knowledge and translating the information into English, Spanish, German, French and Japanese to forestall contentious patent applications.

“India can benefit enormously if it can build a golden triangle between traditional medicine, modern medicine and modern science,” says Raghunath Mashelkar, CSIR director-general. The CSIR has funded three Ayurveda-based projects seeking drug candidates for arthritis, type-2 diabetes and liver disease.

The Ayurvedic system of medicine is nearly 3,000 years old and prescribes remedies for a range of problems, from diarrhoea to contraception. The Sanskrit classics Atharvaveda, Charak Samhita and Sushrut Samhita together describe more than 700 medicinal herbs, cataloguing everything from their taste, appearance and digestive effects to safety, efficacy, dosage and benefits.

For example, the texts refer to neem (Azadirachta indica) as an antidiabetic, Withania somnifera or the Indian ginseng as an antitumour agent, and curcumin — the active ingredient in the spice turmeric — as an anti-inflammatory and anti-diabetic. Scientists are following intriguing leads that curcumin might have antimalarial activity and inhibit the replication of some viruses.

“The Ayurvedic database in classical texts can be used for bioprospecting and new drug discovery,” says Bhushan Patwardhan, coordinator of the CSIR’s arthritis Ayurveda project.

But that task is easier said than done. Some species have become extinct. Time and environmental factors, as well as pesticide and heavy-metal contamination of soils and waters, may also have wrought subtle, but important, alterations in the plant products.

In some cases, there is simply not enough raw material to meet market demand. For example, the Central Drug Research Institute in Lucknow developed an anticholesterol drug, guggul, from the resin of the tree Commiphora mukul. The institute patented the drug in Europe and the United States, and in 1987 licensed it to a Mumbai-based company. The drug brought in about US$80,000 in sales per year, but in 1999, the company was forced to stop making it because the slow-growing tree failed to produce fast enough. The institute has since developed a synthetic version of the drug, which is set for phase III clinical trials in June.

Because plants, in adapting to local conditions, produce the substances at different stages of growth, the herbs must be cultivated and collected in a certain way. The original texts described the specific location, time of year and developmental phase of the plant, and this knowledge was passed down orally. “The best collection practices have eroded with the passage of time,” says Pushpangadan.

With the herbs in hand, scientists must correctly identify the active ingredient, standardize the manufacturing process, and conduct clinical trials to test their effectiveness.

Data mountain

There is no centralized database of the herbs under investigation, but one database of tribal traditional knowledge at the National Botanical Research Institute in Lucknow catalogues more than 10,000 plant species. Of these, fewer than 200 have so far been investigated.

Ayurveda-based drug discovery uses ‘reverse pharmacology’, in which drug candidates are first identified based on large-scale use in the population, then validated in clinical trials. Experts say this approach can cut the time for drug discovery from 12 years to 5 years or less, and for a fraction of the usual cost.

Unlike Jeevani, most herb-derived drugs are widely used across India and cannot be traced back to a particular community. In general, there are few guidelines to ensure that the local population benefits from these drugs, notes Darshan Shankar, president of the Foundation for Revitalisation of Local Health Traditions in Bangalore.

At the moment, even the Kani agreement has problems. The licence agreement expired last year and has not yet been renewed.

T. V. Padma is a freelance writer based in New Delhi.
Breathing life into biology

Mriganka Sur says that life sciences will prosper in India once research and teaching reconnect.

When I was a teenager, I thought I had only two choices — to be a doctor or an engineer. Growing up in Allahabad in the northern state of Uttar Pradesh, students like me were so frequently asked to choose between these two careers that most of us never considered any other options. Becoming a biology researcher did not figure on the list.

There is no question that to capitalize on the life-sciences and biotechnology revolution, India must build excellence in life-science training. In most countries, this is the task of universities. Unfortunately, the Indian university system is in serious decline — acknowledged to be so both within India and elsewhere — and unequal to this task.

As it turns out, I eventually became a neuroscientist, driven mainly by my interest in understanding how the brain works. I never had a university-level course in biology — there were simply none to be taken at the Indian Institute of Technology (IIT) in Kanpur, where I studied electrical engineering as an undergraduate in the early 1970s. But in a sign of the increasing importance of the life sciences, the IITs are beginning to embrace biology. When I went back to give a lecture at the IIT Kanpur a few years ago, I was asked to advise the institute on its newly created Department of Biological Sciences and Bioengineering and a new programme in cognitive sciences.

At the IIT Kanpur, I attended classes taught by excellent teachers and had a few hands-on projects. But the IITs are largely an exception. Most Indian universities are ill-equipped to tackle the complex, interdisciplinary nature of modern biology. Faculty members at both undergraduate teaching colleges and universities offering advanced degrees are largely concerned with teaching, and tend to focus more on theory than on experimental science. But as most scientists can attest, research and teaching are inseparable components of a modern science education.

Many Indian universities don’t have the equipment or the faculty members and staff to give students a solid grounding in techniques and instruments. At some biology departments, even introductory procedures such as DNA extraction are merely described.

This unfortunate division between research and teaching runs deep. The Indian government decided more than 50 years ago to create focused research institutes. The scheme set up distinct priorities: universities would focus on teaching, and the institutes would concentrate on research. That policy led to a handful of excellent scientific institutes but also impoverished university-based research. There is no shortage of funds for university research or teaching laboratories, but a heavy teaching load, an overly bureaucratic system of appointments and promotions, and the lack of infrastructure have all made it difficult to recruit capable researchers.

The institutes, meanwhile, have good research projects, but little teaching. Yet good researchers are also often the better teachers.

Still, many institutes have begun training students by evolving graduate-level courses for small classes. Unfortunately, the top students who train at these institutes often choose to leave India and complete their PhDs abroad — at least in part because few of the centres can match the breadth of education at a first-rate university in the United States or Europe.

What might be done? There is little question that the government should actively support university-based research. Universities need help in upgrading their research infrastructure and laboratories, and in recruiting scientists with dedicated research space and healthy start-up packages. The government could contribute to these costs.

Perhaps federal research grants can include infrastructure costs.

There are signs that the government is responding to these concerns. In March 2005, the Science Advisory Council recommended setting up a National Science and Engineering Research Foundation, on the lines of the US National Science Foundation, to support research in various disciplines. Universities are expected to be important beneficiaries.

As funding for these universities increases, there should be accompanying changes in culture. Research and teaching should be valued as mandatory components of faculty appointments and promotions. Universities should also institute periodic review of the faculty members; this approach is also beginning to find favour in China, a country beset by similar problems.

The particular structure of Indian science also suggests solutions. For instance, funding agencies might consider establishing long-term research faculty positions within universities. New research centres could be closely allied with or even located on university campuses. The researchers would be required to teach in the university, and university students would have access to research labs.

One model for effectively integrating research and teaching already exists within the IITs. These institutes continue to attract the best Indian undergraduates in engineering and the physical sciences, and give them a world-class education. Their success has positioned India as a key player in the IT industry. One small step towards boosting the life sciences may be to encourage the IITs to expand their biological sciences curriculum. But that cannot be the only solution, if only because a wider transformation is needed.

Innovation in universities is part of a broader theme in how a society educates not only its elite but all of its citizens. A hard look at education in the life sciences is particularly urgent for a country such as India, which has both a strong need for development and the ambition to match it.

Mriganka Sur is head of the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology.
Coming home

Reagents may be slow to arrive, but the freedom to explore his own research interests more than compensates. **Satyajit Mayor** is thriving in India.

"I can never be the same as doing science in America." This was the near-unanimous response from my peers when, in late 1995, I announced my decision to move back to India from the United States. By then, I had spent nearly 11 years in America, first as a graduate student at Rockefeller University and then as a postdoctoral fellow at Columbia University.

Like most expatriates who long to return home, I had planned for many years to return to India — but I kept putting it off. I worried that my career in India would become marked by obscurantist science, an ossified research set-up and cash-strapped institutes; that I would be surrounded by mediocre science and scientists; and that I would have to wait for weeks for supplies that can be summoned in New York within a day.

Happily, I was wrong on most counts. And I’m not the only one. Like me, many other researchers are choosing to return home, and they’re leading productive lives at the many small-sized institutions that are committed to competing in the international arena.

The National Centre for Biological Sciences (NCBS) in Bangalore recruited me in 1995, and I have remained here ever since. The centre was set up in 1992 as an arm of the Mumbai-based Tata Institute of Fundamental Research. The founding director, noted *Drosophila* geneticist Obaid Siddiqi, wanted to establish an institute where a diverse group of people with distinct approaches to biology could do world-class research. I knew from the beginning that this would be a good place.

Since its launch, the institute has moved into a much bigger campus and hopes to grow from its current 15 research groups to a full capacity of around 40 teams. Together, NCBS researchers published 60 papers in 2004, including 18 in high-impact journals such as *Nature* and *Cell* (see table, left).

The institute's current director, K. Vijay-Raghavan, is generous to a fault, and accommodates the most outrageous of whims of his colleagues in the interest of furthering science. Most laboratories at the institute are engaged in research on different biological scales — from understanding the structure of molecules to the evolution of behaviour. My own lab aims to unravel the molecular mechanisms of endocytosis, the process by which cells internalize viruses or molecules, using a multidisciplinary approach that combines biology, physics, and chemistry.

Being a researcher in India is not as difficult as I had expected. In some ways, my transition from being a privileged graduate student at Rockefeller University to a postdoctoral fellow at Columbia University was more of a culture shock than my move to the NCBS, where the scope of my research is limited only by my imagination. More difficult was the adjustment to life in an Indian city after living in New York. I was also not looking forward to confronting the depressing political reality in India at the time. (Happily, things have changed for the better, thanks to India’s democratic tradition.) But exciting scientific interactions at the NCBS and elsewhere in India have been more than adequate compensation for these travails.

**Beating bureaucracy**

When I joined the NCBS, my area of research, cell biology, was not yet the focus of much study there: protein structure and developmental neurobiology were more in vogue. I had trained almost entirely outside India so I had very different expectations when I arrived, but I was able to shape my environment as much as it shaped me. For example, my colleagues and I have helped to create an administrative structure that is both efficient and responsive to our needs. This is something most scientists in developed countries might take for granted, but revising the old bureaucracy-ridden model is an important step forward for Indian science.

Upon arrival, my priority was to set up my laboratory, and the NCBS seemed to share this emphasis, something that is rare at most Indian institutes. Still, some of my fears were legitimate. When I was at Columbia University, for instance, I could simply pick up the phone and have reagents instantly delivered to my bench. Here, it can take up to four weeks depending on where the manufacturer is located.

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**PUBLIC RECORD OF THE NATIONAL CENTRE FOR BIOLOGICAL SCIENCES**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. of publications</th>
<th>Publications in high-impact journals</th>
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<tbody>
<tr>
<td>1998</td>
<td>23</td>
<td>Nature (1)</td>
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<tr>
<td>1999</td>
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Another formidable challenge is convincing customs officials that my high-resolution cameras need not be exposed to the elements while numerous public holidays pass by. Things have changed for the better as suppliers have set up shop in or near Bangalore, but there is much room for improvement.

For the majority of Indian researchers, publication in prestigious international journals is as much a marker of success as it is elsewhere. But scientists here have not been able to fully meet this goal. Most of my colleagues in India believe that this is partly, the result of a bias, conscious or unconscious, against Indian science. The critical mass of biologists — except perhaps in protein chemistry (see page 494) — in India is too small to have any visibility in international publishing. The lack of name recognition may make it easier to dismiss exceptional and controversial work from unfamiliar institutions.

Manual work
At many of the biology-based institutions in India, almost all the work is done by graduate students, and they can take up to four years to become productive. This is the result of an educational system that prevents students from getting their hands wet, partly because the system does not value experimental training and partly because of a genuine lack of resources. One reason for this is a bias against manual work among the elite classes who populate the universities. Fortunately, this seems to be changing (see page 487).

Although the graduate-student pool generates a group of committed researchers, the lack of a vibrant postdoctoral research culture is the sign of an unsophisticated research community. Some institutions in India are beginning to recruit postdocs from around the world, albeit slowly. But even among Indian students, going abroad to train is still the most attractive option. The handsome salaries offered by research positions in Europe and the United States are no small factor in their decision. More attractive salaries would go a long way to retaining researchers in India.

At 1.1% of the gross domestic product, India’s budget for science is woefully inadequate. But the government has pledged to increase this to 2% by 2007. Already, funding opportunities for biological sciences in India are at an all-time high. Several agencies fund projects and any well-structured proposal has a high chance of getting funded.

In addition, researchers have access to international agencies. The arrival of the Wellcome Trust in India six years ago wooed many young talented researchers back to India (see ‘Wellcome funding’, below). Such international agencies have helped bridge the gap between the salaries in India and more developed countries.

Wellcome Trust fellows are required to provide frequent research reports and attend meetings to evaluate progress, which ensures that they stay focused. A major flaw in India’s system is that the funding agencies seem to expect little intellectual return on their investment, which can breed complacency.

One of the biggest attractions as a scientist in India today is the freedom to take on unusual and innovative projects without much interference. Because the pool of active researchers is small, it fosters truly multidisciplinary collaborative links. I have been able to forge meaningful collaborations with a condensed-matter physicist, a fruitfly geneticist interested in neuronal conduction and a physiologist of the immune system.

India’s biological research enterprise requires a broad and visibly multidisciplinary scientific base. Institutions such as the NCBS can help accomplish this goal. Another ten similar institutions could completely transform the nature and quality of biological sciences in India. If these institutes then form productive alliances with universities, they could tap into India’s vast student pool. At the very least, this could boost the woefully underfunded and often stifling university departments. The much touted biotech revolution in India may even acquire well-trained scientific personnel and a semblance of reality.

In an encouraging development, the government in February this year announced a US$250-million National Science and Engineering Research Fund to fund basic research in India. The goal is to establish two integrated universities to teach and train a new breed of basic scientist, the most important resource for a productive scientific future. Satyajit (Jitu) Mayor is an associate professor at the National Centre for Biological Sciences, Bangalore.

Wellcome funding

Many of Indian biology’s rising stars, such as Satyajit Mayor (see main text), are recipients of the Wellcome Trust International Senior Research scheme.

These fellowships, awarded for five years and renewable for another five, are highly coveted because of their size — bigger than the budget of the science departments in some Indian universities — and because they can be used flexibly. In 2004, 14 scientists from India were interviewed for the grants; all won.

Unencumbered by the pressure to raise their own money, many of the fellows are doing very well. Utpal Bhadra, a fellow at the Centre for Cell and Molecular Biology (CCMB) in Hyderabad, has co-authored six papers in high-impact journals, including Science, Nature Genetics and Molecular Cell, since his return to India in 2002. His book on RNA interference, written with his wife, a 2005 fellow, is to be published by the Cold Spring Harbor Laboratory Press. Sanjeev Galande, a fellow at the National Centre for Cell Sciences, has also published six papers in prestigious journals in the past four years.

Rajan Sankarnarayanan, another fellow at the CCMB, used his Rs33 million (US$800,000) award to set up a world-class crystallography lab to study protein structure with equipment that would otherwise have been out of his reach.

“This kind of fellowship has helped many young scientists, including myself, to return after postdoctoral training abroad and establish their own laboratories in the home country,” says Sankarnarayanan.

Altogether, 37 Indian biomedical researchers have benefited from the grant. The trust has also supported researchers in South Africa since 1992 and in Central Europe since 2002. These countries shared 15% of the funding; the rest was earmarked for scientists from Britain. But from 2005, all applicants will have to compete with UK scientists.

K. S. Jayaraman
Rivalry and red tape

Researchers are suffering as a result of the conflicts between funding agencies. T. V. Padma uncovers plans to heal the rift.

Pradeep Seth has given up. For nearly two years, Seth, a microbiologist at the prestigious All India Institute of Medical Sciences (AIIMS) in New Delhi, has been awaiting word on his HIV vaccine candidate from the health ministry.

Seth's vaccine research was funded by the Department of Biotechnology (DBT), part of the science ministry. He published his work in peer-reviewed journals and received positive feedback from several evaluation committees. In March 2003, the DBT gave him the green light to form a partnership with an Indian company and manufacture the vaccine for phase I human trials.

Everything went according to plan. A committee at the AIIMS helped Seth select an industrial partner and write a licence agreement. The institute's legal and financial departments approved the agreement. Then, in December 2003, an over-cautious AIIMS director sought additional approval for the agreement from the health ministry. Seth has been waiting for that approval ever since.

Awaiting approval: Pradeep Seth waited for more than two years for the go-ahead from the government for phase I trials of his HIV vaccine.

The quality of the potential vaccine does not seem to be the problem. The healthy ministry formed a committee to review the vaccine in December 2003. But before it made a decision, India headed for national polls, and a new government took charge in May 2004. "It was back to square one," says Seth. A new committee then recommended in November 2004 that trials on the vaccine should proceed without further delay. Then the health secretary, who had to okay the licence agreement, retired. "Again back to square one," says Seth.

Finally, a third committee reviewed the vaccine in February 2005. This committee, led by Nirmal Kumar Ganguly, director-general of the Indian Council of Medical Research (ICMR) — the research arm of the health ministry — recommended on 29 March 2005 that the trials should proceed. By then Seth had almost retired.

Lack of coordination

Seth's story is well-known in Indian academic circles. Some say the story is a tragicomic case of classic Indian bureaucracy. But others say the events are no accident. Seth's vaccine did not fare well because of a deep-seated rivalry between the DBT, which funded his research, and the ICMR, they say. "Most DBT-funded projects in the AIIMS have met a similar fate," says Seth.

There are several branches of government that fund biomedical research, but money comes primarily from the health ministry, which finances research through the ICMR, and the science ministry, which oversees the DBT, the Department of Science and Technology and the Council of Scientific and Industrial Research (see graph).

Each agency has — or is at least supposed to have — a well defined role. For example, the Department of Science and Technology looks after basic research; the DBT focuses on the development of biotechnology products and processes; and the ICMR funds projects in epidemiology and clinical research.

In theory, the health and science ministries would coordinate research. "In practice, however, overlaps do take place," says Martanda Sankaran Valiathan, former president of the Indian National Science Academy.

These glitches occur despite representatives from funding agencies sitting on each other's committees and asking applicants to note whether they receive funds from elsewhere.

Some projects can be neatly classified as basic or clinical, but increasingly there are many projects that are 'applied'. Stem-cell research falls squarely into this hazy overlap.

No single government agency in India has been assigned responsibility to licence or monitor stem-cell work. As a result, the DBT and the ICMR each issued guidelines — the DBT in 2001 and the ICMR in 2002 — without consulting each other. The result was a plethora of public- and private-funded institutes that joined the stem-cell bandwagon.

Researchers at Nutech Mediworld, a private clinic in Delhi, say they have used stem cells to successfully treat paralysis in 24 patients since May 2003; their work is as yet unpublished. P Venugopal, a surgeon at the All India Institute of Medical Sciences in Delhi has used bone-marrow derived stem cells to repair damaged heart muscles (see Nature 434, 259; 2005). And the L. V. Prasad Eye Institute in Hyderabad has since 2001 used limbal stem cells to repair damaged corneas in 260 patients (V. S. Sangwan et al. Biosci. Rep. 23, 169–174; 2005).

The competition between the DBT and the ICMR in particular has been the focus of much discussion among researchers. "Greater collaboration between agencies is a critical issue," says secretary of the DBT Maharaj Kishan Bhan. "Our research efforts are getting fragmented because of this lack of coordina-
A waiting game

Another area of researchers’ lives that could be improved is that of paperwork. For example, to get a grant approved, Indian scientists have to be prepared to wait for more than a year while their application is processed, and months more to get the money after approval. The funds go to the institution and not to the investigator, so additional delays occur during the transfer of money to the researcher.

Researchers have to submit nearly 30 copies of their proposal to funding agencies such as the ICMR. So cumbersome is the red tape that in January 2005, at the opening of the science congress in Ahmedabad, prime minister Manmohan Singh lamented the “tyranny of bureaucracy” in Indian agencies. He went on to ask whether India has “allowed bureaucratic systems and patron–client relationships to stifle creativity” and “scare away” young researchers.

“Most of the red tape is due to the fact that there are no serious consequences for incompetence,” says Sandip Basu, director of National Institute of Immunology in Delhi. “It is not easy to take severe disciplinary action, and all jobs are until retirement,” he says.

Some delays are entirely avoidable, Basu adds. These are the ones agency chiefs are committed to cutting down. Some researchers are reporting that recently submitted proposals to the Department of Science and Technology and the Council of Scientific and Industrial Research cleared in six months. What’s more, the process required only two hard copies: the rest was handled through e-mail.

But this may have all come too late for Seth whose last working day was 30 April. “I am through with it,” Seth says.

T. V. Padma is a freelance writer based in New Delhi.

A TOUGH JOURNEY

To outsiders, Vijaylakshmi Ravindranath’s story might seem a resounding success. In 2000, she was appointed director of the nascent National Brain Research Centre in Manesar, on the outskirts of New Delhi.

But her achievement did not come easily. When Ravindranath was a postdoc at the US National Institutes of Health, her husband, also a scientist, remained in India. She initially took her two-year-old son with her, but, unable to arrange for his care when she was in the lab, she sent him to be looked after by her parents. “I had to be away during two critical years of my son’s childhood,” she recalls.

Twenty years later, she was once again faced with a difficult choice. The offer to head the new centre was a rare opportunity, but it meant a five-year separation from her husband and son. “Had my husband and son not cooperated, it would have been impossible,” she says.

Ravindranath is one of the lucky few. Unable to juggle professional and domestic demands, and sometimes coping with nepotism and sexual harassment, most Indian women scientists give up early in their careers. According to a 2004 report of the Indian National Science Academy (INSA), only nine of 398 Shanti Swarup Bhatnagar awards, India’s highest honour for science, went to women. Within the INSA, women have won only 14 of the academy’s 502 awards and medals, and no woman has ever led the academy.

Like their counterparts worldwide, Indian women scientists fare better in biology than in engineering or physics. In 2000, women accounted for 32% of medical students, compared with 16% in engineering. But, as elsewhere, there is a steep drop-off in women at graduate level. Many of those who continue opt for a career in medicine or teaching, rather than research, says Manju Sharma, former secretary of the Department of Biotechnology and co-chair of an international advisory panel on women scientists.

Apart from the usual factors, such as marriage and lack of adequate childcare, Indian women also have to endure the country’s staunch patriarchal culture. Many complain that male colleagues do not treat them as peers and often assign them to reception committees or to choosing menus for conferences.

Women also face considerable bias in the interview process, says Sharma, who has served on the interview committees of several national institutes. “I have noticed a tendency to ignore the excellent career records of women scientists when it comes to selecting top positions,” she says.

The government is beginning to take action. In 2003, the Department of Science and Technology initiated a scheme to offer fellowships to women whose careers were interrupted by their husbands’ geographical moves. More than half of the 2,000 applicants were from life sciences.

Women scientists particularly need assistance when they are struggling to balance their early career with a growing family, says Ravindranath. “If the woman can tide over the period of marriage and child rearing, a critical mass of women scientists can develop in biology,” she says. “Today, my son and husband are among the proudest and happiest about my success.”

T. V. Padma
Among the best

India’s life-sciences institutes are rewriting the rule books for research. K. S. Jayaraman finds that they are focusing on higher standards and enterprise.

Just two years ago, the tree-lined roads on the campus of the Indian Institute of Science (IISc) in Bangalore were a joggers’ paradise. The only sounds were those of rustling leaves and chirping birds. These days, blaring horns and speeding Toyotas are more the scene, occasionally forcing terrified pedestrians into the wedge-shaped drains on the sides of the roads. “Everyone here is in hurry,” says S. Vijaya, a professor of microbiology at the institute.

This flurry of activity is a result of a radical culture change at the IISc, widely considered India’s premier scientific institute. Fourteen companies — including Belgium’s Janssen Pharmaceutica and New Jersey-based Novozymes Biologicals — now rent laboratory space on campus. Researchers at the IISc have acted as consultants for 161 companies and completed more than 100 projects in the past ten years. And in the past three, five professors have launched their own companies.

The Indian Department of Biotechnology is encouraging this trend by allowing faculty members to hold positions in industry and academia simultaneously. It has earmarked 30% of its US$105-million budget for 2005–06 to such partnerships.

A similar scene is being played out all over the country. With nearly 450 faculty members in disciplines ranging from biochemistry to metallurgy, the IISc is the largest and the most established Indian institute. But a handful of smaller life-sciences institutes that have sprung up in the past decade are also rewriting the rules of Indian research. “We have succeeded in setting higher standards for ourselves and achieving them,” says G. C. Mishra, director of the National Centre for Cell Sciences (NCCS) in Pune.

Not everyone is happy with this change. For many Indian researchers, making money from science is an uncomfortable concept. Hindu mythology even holds that Lakshmi, the...
Leading the way: the Indian Institute of Science in Bangalore is the most productive of India’s life-science institutes.

goddess of wealth, and Saraswati, the goddess of learning, cannot coexist.

“Half of us would be happy teaching and publishing papers,” says P. N. Rangarajan, associate professor of biochemistry at the IISc. But the other half are making the most of this new opportunity.

Rangarajan is firmly in the latter group: this year he won an award for transferring the DNA vaccine he developed against rabies into a commercial setting. His vaccine can be stored at room temperature and so is ideal for tropical countries. The IISc licensed the technology to Hyderabad-based company Indian Immunologicals.

But this achievement came at a price for Rangarajan. His promotion was delayed by two years because the number of papers he published declined during the time he spent with his industrial partner.

Measuring success

This attitude is slowly changing, but many administrators still insist that academic pursuit should be the faculty’s first priority. “Our basic objectives continue to be research and teaching,” says G. Mehta, director of the IISc. “If the faculty finds time to hold hands with industry, that is welcome.”

Some researchers feel that this attitude is a little short-sighted. “We should have a different yardstick for assessment,” says Govindarajan.

Homogeneous than the Icelandic population, says Partha Majumdar, head of the human genetics unit at the Indian Statistical Institute (ISI) in Kolkata, who compared published genetic data of Icelandic populations with those of ethnic Indian groups.

In India, it is possible to study genetic variation both within and between communities, Brahmachari adds. He is coordinating a five-year US$5.8-million project that includes researchers from his institute and five others under the Council of Scientific and Industrial Research. Launched in 2003, the Indian Genome Variation consortium aims to map genetic markers for diseases such as diabetes, cancer and heart disease. The ISI will analyse the data from the project and help choose sample populations for the studies.

In 2003, the International HapMap Project, which aims to find genes associated with human disease and response to pharmaceuticals, asked Majumdar for samples from some Indian ethnic groups. But the ISI does not have the technology to be a proper partner in this project, and Majumdar says he declined because he did not want only to supply samples.

The Indian project’s goal is to collect blood samples from 15,000 individuals drawn from different communities across the country, select about 1,000 genes relevant to complex diseases common in India and assess any differences in drug response. The scientists plan to study candidate genes reported by other groups as well as any new ones that crop up.

The team plans to record DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. These are known as single nucleotide polymorphisms or SNPs. The group also hopes to note repeats of nucleotides and compare their frequency across different groups. Brahmachari’s team has already collected samples from more than 40 populations, but because the report is unpublished, he declined to reveal further details.

Other genomics projects are also under way in increasingly well-equipped labs at the Institute of Genomics and Integrative Biology, the Centre for Cellular and Molecular Biology (CCMB), the Centre for DNA Fingerprinting and Diagnostics in Hyderabad, the Indian Institute of Science in Bangalore and the University of Delhi.

In November 2004, India agreed to take part in a pan-Asian initiative to study genetic diversity and similarities in Asia. The ten-nation study, an initiative of the Pacific chapter of the Human Genome Organisation, is slated to begin later this year. Researchers at the Hyderabad-based CCMB are also studying disease susceptibility in various castes and tribes. In collaboration with the Anthropological Survey of India and 15 universities, the researchers have collected more than 9,000 DNA samples from 130 groups.

From these samples, scientists have already identified genetic diseases that are particularly prevalent among certain groups, says Kumarasamy Thangaraj, a researcher at the CCMB.

For example, the Onges tribe has dwindled to only 98 people from 700 in 1858. Genetic analysis of 46 members of the tribe has revealed 23 mutations in the mitochondrial genome and deletions of some Y-chromosome genes needed for sperm production.

“It is astonishing that in several populations, the load due to genetic diseases is so high it is leading to their extinction,” says Thangaraj.

T. V. Padma
Basic research in the life sciences has not been India’s strong suit. But in one field — protein science — Indian researchers have made their mark.

India’s love affair with proteins began more than 50 years ago, when G. N. Ramachandran, a physics professor at the University of Madras, and his colleague, G. Kartha, used X-ray data analysis to unveil the triple-helical structure of collagen, one of the most abundant proteins in mammals.

The X-ray machine was primitive, and Ramachandran performed painstaking manual calculations to work out collagen’s structure. He also came up with a formula, later dubbed the Ramachandran plot, to predict the conformation of proteins. During his career, he trained several biophysicists who worked with him first in Madras, now called Chennai, and then at the Indian Institute of Science (IISc) in Bangalore.

Around the same time, teaching and research in biochemistry gained ground in India, and scientists from both disciplines began to collaborate. “India could thus produce groups of people and enough institutional expertise to work on both protein physics and protein chemistry, which proved to be an advantage,” says Padmanabhan Balaram, a protein physicist and chairman of biological sciences at the IISc. In the 1980s, the field received a further boost when government agencies began providing funds to buy equipment for selected centres.

Work on proteins also suits the research culture. Indian scientists prefer projects that rely more on individual creativity and competence because they fear large groups will detract from individual recognition, says Govindarajan Padmanaban, scientist emeritus at the department of biochemistry at the IISc. “Indian scientists on the whole do not integrate in large groups,” he says.

Because protein research rarely requires large interdisciplinary collaborations, it has remained a popular choice among Indian scientists. Countries around the world may be able to benefit from India’s expertise. “With rising costs and the closure of some chemistry departments in the United States and Europe,” Balaram says, “India could become a destination for outsourced chemistry research and development, including theoretical work such as the study of protein dynamics and computer modelling for drug design.”

T. V. Padma

Highly respected: Indian scientist G. N. Ramachandran (first row, centre) made a significant contribution to the field of protein science. Here, he is shown sitting next to his wife (first row, second from left). Ramachandran is talking animatedly with S. Ramasesham (first row, fourth from left), another eminent crystallographer. G. Kartha, the co-discoverer with Ramachandran of the triple-helical structure of collagen, is seated in the fourth row (far left).

Padmanaban, a biochemist and former director of the IISc, who has discovered a potential drug target for malaria. “Publication is not everything,” he adds.

The rules are a bit looser at the government laboratories, such as those under the Council of Scientific and Industrial Research (CSIR). In 2000, the CSIR launched a programme to promote partnerships with industry.

For instance, since 2001 Mumbai-based Nicholas Piramal India has been paying the CSIR’s Institute of Genomics and Integrative Biology (IGIB) in Delhi US$460,000 each year as a ‘knowledge’ fee. The arrangement allows the company to develop any leads the institute’s researchers find. The alliance has already resulted in two joint patents. A potential drug against tuberculosis that has shown promise in animal studies is the outcome of a similar alliance between Mumbai-based Lupin Laboratories and four CSIR institutes.

To promote technology transfer, the IISc has launched an ‘incubation’ centre, where faculty members help students to develop commercial applications. The institute also supports scientists who launch biotechnology companies by granting them ‘entrepreneurial leave’, making it a popular partner for multinational companies. General Motors has invested US$1.4 million and Boeing US$500,000 in research at the IISc.

The IISc is careful to accept only projects that involve innovative research. The Society for Innovation and Development, the commercial arm of the institute, has turned down about US$20 million in projects because they

<table>
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<th>COMPARISON OF FOUR HIGH PROFILE INDIAN LIFE-SCIENCE RESEARCH INSTITUTES IN 2004–05</th>
<th>No. of faculty members</th>
<th>No. of publications</th>
<th>No. of patents</th>
<th>No. of faculty members educated abroad</th>
<th>Percentage of faculty members trained abroad</th>
</tr>
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<tbody>
<tr>
<td>Indian Institute of Science, Bangalore</td>
<td>450</td>
<td>1,367</td>
<td>25</td>
<td>129</td>
<td>98</td>
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<tr>
<td>National Centre for Cell Sciences, Pune</td>
<td>24</td>
<td>37</td>
<td>6</td>
<td>16</td>
<td>96</td>
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<tr>
<td>Centre for Cellular and Molecular Biology, Hyderabad</td>
<td>88</td>
<td>111</td>
<td>15</td>
<td>20</td>
<td>80</td>
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<tr>
<td>National Centre for Biological Sciences, Bangalore</td>
<td>21</td>
<td>49</td>
<td>Nil</td>
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lacked research content, says S. Mohan, the society’s chief executive. “Even then, the demand from companies is so great we cannot cope,” he says.

Some partnerships with industry are providing much-needed training for young scientists. For example, Hyderabad-based Bharat Biotech has trained nearly 500 interns in biotechnology. In addition, 12 students of Jawaharlal Nehru Technological University in Hyderabad are doing their graduate work at the company.

Critical mass
With more than 1,300 papers published in peer-reviewed journals last year, the IISc is the most productive of the Indian institutes (see table, left), and continues to enjoy the government’s favour. In February 2005, the government gave the institute a massive grant of US$24 million.

But in the past ten years, a handful of other institutes have begun to make their mark. The National Centre for Biological Sciences in Bangalore, an offshoot of the famous Tata Institute of Fundamental Research in Mumbai, produced India’s first paper to be published in the high-profile journal Cell just four years after it moved to its own building in Bangalore. The institute’s faculty members were recruited almost entirely from the United States, and they work under a US-style contract system: scientists are hired for five years and their performance is periodically reviewed by the institute’s research council. One contract has already been terminated — the first time a publicly funded scientist in India has been sacked for underperformance.

But the model is unlikely to catch on. “Indian scientists want secure jobs,” says Ranrarajan. “If there was a poll, 80% would opt for security in preference to contract jobs at higher salary.”

As biotech companies continue to proliferate, academic centres will find it difficult to hold on to scientists unless they raise salaries by an order of magnitude, warns C. N. R. Rao, former IISc director and the prime minister’s science adviser. Rao says there of his students joined General Electric’s research labs in Bangalore at a salary of US$1,400 per month, twice what a professor at the IISc can expect to earn.

Some institutes offer attractions to compensate for the lower salaries. “What they need is freedom and a conducive atmosphere,” says Lalji Singh, director of the Centre for Cellular and Molecular Biology in Hyderabad.

NCCS director Mishra says his institute’s high productivity — 35 papers were published in high-impact journals in 2004 — helps to attract good scientists. The NCCS has grown from 13 faculty members in 1995 to 25 in 2005 (see table, opposite); all except one are Indians who trained abroad. In the early years, Mishra says, he had to go to the United States to recruit scientists, but now he gets about one overseas application each week.

Lost in translation
India’s life-science institutes are improving at a rapid rate (see ‘Strength in numbers’, previous page, and ‘Strong bonds’, opposite). Already, Indian scientists are more productive per dollar invested in their research than their counterparts worldwide (see tables, above). But overall, India lacks a critical mass of competent scientists in basic and clinical research, notes Sandip Basu, director of the National Institute of Immunology in New Delhi. As a result, there is limited collegial interaction and unreliable peer review. “The resulting isolationist, nepotistically inclined atmosphere does no good to the cause of fostering high-quality research in the country,” he says.

The country’s medical schools lack the infrastructure and the faculty staff to train researchers. A quarter of India’s 229 medical colleges have never published research reports in indexed journals; most clinical research comes from just three medical institutes.

“We have a fair amount of curiosity- and individual-driven research,” says Maharaj Kishan Bhan, secretary of the Department of Biotechnology. But without clinical researchers to translate advances into treatments, “the bulk of Indian research in basic science is lost,” he says. “The whole chain does not function in an orderly fashion.”

Bhan says what’s needed is an institute for translational research where basic-science researchers and physician researchers can collaborate on finding solutions to India’s public health problems. It would focus on developing simple, low-cost technologies that can be used in settings where the resources are poor. “We need to build one or two such new technology-focused institutes,” he adds.

In the United States, the biotechnology sector accelerated rapidly when scientists moved from academia to industry, patenting their discoveries. “The opportunities that are unfolding in India are breathtaking,” says Ragunath A. Mashelkar, director-general of the CSIR.

K. S. Jayaraman is Nature’s India correspondent.
The coming epidemic

A staggering 5.1 million people are estimated to be HIV positive in India. Apoorva Mandavilli finds a country on the brink of a crisis.

Our son was born in June 1998. He was healthy but after eight months, he had diarrhoea and fever all the time. He was in the hospital many times. The sixth time, they diagnosed him with AIDS. That was when we found out that my wife and I have HIV.

Our son died 12 July 2002. I also started to get sick. I didn’t take my medicines regularly; they didn’t tell me not to do that. Now my health has become worse. I haven’t worked in six months. We’ll be paupers. I don’t know what we’re going to do.

— Suresh, air-conditioning technician

Suresh is sitting in a small, dark room at an AIDS clinic in the southern Indian city of Chennai. This city is where the first cases of HIV in India were discovered in 1986 after a police sweep of sex workers. Nearly 20 years later, there are an estimated 5.1 million cases in India, a number second only to that in South Africa. The difference is that in India the epidemic has not yet peaked. According to the CIA, the number of cases in India could top 20 million by 2010.

The people hit by AIDS in India are not the ones you would expect. About 86% of cases are a result of sexual transmission, most of it heterosexual. Intravenous drug use accounts for only 2.4% of infections, except in Nagaland and Manipur, two states where HIV infection is highly prevalent. The earliest cases appeared in high-risk groups: among the country’s 3 million sex workers or the 5 million truckers who haul the virus up and down the highways. But increasingly, the people who are flooding hospitals are men like Suresh, and their wives and children.

Like many Indian men, Suresh visited sex workers before he got married. He is in his thirties, but looks at least 20 years older. He is thin, with large sores on his lips. His wife Sumithra Devi was once near death, with a T-cell count of 40; a person is said to have AIDS once their T-cell count drops below 200. Afraid to tell anyone they have AIDS — their family believes their son died of tuberculosis — they travel nine hours from Kancheepuram to Chennai to visit YRG Care, a non-profit clinic.

The clinic enrolled Sumithra first in a clinical trial and then in a Global Fund to Fight AIDS, Malaria and Tuberculosis programme that provides antiretroviral drugs. She looks healthy now, and her T-cell count has shot up to 1,000. But Suresh, who is resistant to the drugs that the programmes provide, is desper-ate for newer treatments — and the money to buy them. “It’s too late for me,” he says.

AIDS is a big problem in India but we have been able to keep it in place so that it doesn’t become a bigger problem. We are not going the South Africa way.

— Nirmal Kumar Ganguly, director-general, Indian Council of Medical Research

In May this year, the Indian government announced that during 2004, there were just 28,000 new cases of HIV infection, down 95% from the previous year — proof, it said, that its strategies are working. But even in the United States there is an estimated 40,000 new cases each year, says Kevin Frost, director of TREAT Asia, a network of HIV/AIDS clinics and institutions. “So do you believe that Indian number?” he asks. “Of course not, that would be ridiculous.”

S. Y. Quraishi, director-general of the National AIDS Control Organization (NACO) says that the figures were collected in exactly the same way as the previous year. “Tell me, what can we do? This is the best possible estimate,” he says.

Compared with South Africa, where the prevalence of HIV is 21.5%, India’s prevalence is just 0.91%, Quraishi notes. That is less than the 1% generally considered to be the tipping point, beyond which the epidemic will escalate out of control. It took just seven years for South Africa’s prevalence to rise from 1% to 20%.

“Considering that our prevalence has been kept to less than 1%, that shows that our strategies have been on the right track,” Quraishi says. “It’s not by sleeping that we’re not South Africa. Obviously we did something.”

But the statistics are sobering (see graphic, opposite). Six states in India already have a prevalence greater than 1%, and in 2004 the number of high-prevalence districts jumped from 49 to 116. Even in the low-prevalence or ‘highly vulnerable’ states, as they are now dubbed, there are pockets where more than 4% of adults are infected. “The epidemic is progressing to the tipping point, there’s no doubt about that,” says Ashok Alexander, director of Avalon, the Bill & Melinda Gates Foundation’s AIDS initiative in India.

Some experts say that the new administration, which in April 2004 replaced the previous right-leaning government, could yet turn things around. NACO’s strategy is to reach high-risk groups — particularly sex workers and truck drivers — and scale up programmes that have proved successful. Over the next five years, it plans to expand its 670 voluntary testing sites to 24,000 and increase the number of people on antiretroviral therapy from an estimated 8,000 to 188,000 (see ‘Seeking care’, opposite).

But in the world’s most populous democracy, good intentions don’t go very far. Despite doubling its AIDS budget since 2003–04, India still only spends about 29 US cents per person on AIDS. In contrast, Uganda, credited with curbing its AIDS crisis, dedicates US$1.85 per person. Already, India accounts for more than 13% of the world’s AIDS burden but with its prevalence so close to the tipping point, the stakes are high. “Overall,” says Frost, “the Indian government’s response has been pathetic and not what it needs to be for an epidemic of this size.”
I saw people with AIDS die. That’s when I started getting scared. I have been teaching other sex workers about AIDS, telling them to use condoms. Now clients also want to put on condoms. They are available at medical shops. But I know where to get them for free.

— Padma, sex worker

In Mumbai, the bustling metropolis on India’s west coast, there are nearly 100,000 sex workers. Volunteers from non-governmental organizations (NGOs) walk through the streets of Kamathipura, the red-light district, handing out condoms and leaflets.

But in the southern states, where prevalence is highest, there are no red-light districts to canvass (see ‘The epicentre’, overleaf). Instead, sex workers — many of whom are married women — work out of their homes, hotels or on the highways, earning themselves the nickname ‘highway queens’. Some towns, such as Peddapuram and Amalapuram in the state of Andhra Pradesh, are “like one big red-light district”, says Ashok Babu, a programme manager for the AIDS Prevention and Control Project in the neighbouring state of Tamil Nadu. “For US$230, you can stay there for one month and be treated like a mappillai,” he says, meaning a son-in-law, who is treated like a prince by the girl’s family. In Andhra Pradesh, HIV prevalence jumped from 1.25% in 2003 to 2.25% in 2004. Experience has shown that the best way to reach these unconventional sex workers is through their peers. At the Community Health Education Society, an NGO in Chennai, ‘peer educators’ such as Padma explain to the women how to use a condom, the difference between HIV and AIDS, and why they are more at risk of getting infected. But the message is cleverly delivered through games, songs or as a cost–benefit analysis of, for instance, the amount of money squandered on abortions and treatments for sexually transmitted diseases. “When you talk to them just about AIDS, they get bored,” says Pinagappany Manorama, a physician who runs the NGO.

In some ways, sex workers are now better informed, and more empowered, than

## SEEKING CARE

When you’re trying to manage an AIDS epidemic and you have limited resources, preventing infection is the logical priority. But where does that leave those who are already infected?

Treating people with AIDS is not easy. At the very least, it requires trained medical staff and the resources to make sure patients take the drugs on time. Nobody knows that better than the doctors at Tambaram Hospital.

Built in 1928 as a sanatorium for patients with tuberculosis, the government centre is 45 km outside Chennai and has more AIDS patients than any other Indian hospital. There are often more than 900 inpatients for its 776 beds, so some have to sleep on the floor. Every hallway is flooded with patients who look skeletal, with shrunk limbs and sallow skin. Outside the wards, hairy black pigs roam beneath drying rancid smell of sewage.

The hospital was one of eight government centres that together were meant to roll out antiretroviral drugs (ARVs) to 100,000 people over five years. In the first year, which began April 2004, it treated fewer than 1,000. “From the outside, you may think it is a low number, but for people working here, there are a lot of problems,” says S. Rajasekar, the hospital’s deputy superintendent. Despite repeated requests, he says, the centre has the same resources it did in 1993, when it had just two HIV-positive patients. In 2004, it saw 14,991 new patients and had 140,000 hospital visits from HIV-positive patients. “With just 25 doctors,” says Rajasekar. “Amazing, right?”

By June 2005, government centres, including Tambaram Hospital, had doled out ARVs to 8,000 people. In the same time, since April 2004, small private and non-profit clinics reached an estimated 30,000 sufferers. But these clinics are in a constant struggle for survival.

One such centre is the Naz Foundation’s orphanage in New Delhi. Of the 24 children there — ranging in age from 19 months to 17 years — 10 are on ARVs. Despite one child dying two years ago, only the oldest one knows that she is HIV positive. To spare the children from stigma, their status has also been kept secret from their teachers and neighbours.

One child’s monthly supply of ARVs can cost about Rs900 (US$20). The home was funded by the Gere Foundation until March 2005, but since then money has come almost entirely from small, private donations. “Care is something no traditional donor wants to fund,” says the centre’s director, Anjali Gopalan. “They see it as a black hole, as one donor told me. There’s no return on the dollar.”

Scrambling to treat their patients, doctors at some clinics use medicines that are past their expiry date; others bring free drugs they are given in the United States or elsewhere. Staff at the YRG Care Clinic in Chennai last year began asking people to donate just $10 each. “It’s always beg, borrow, steal, donations, fundraiser. That’s how we get funds for care,” says Suniti Solomon, who runs the YRG. “We cannot save the millions out there. The government has to do that.”

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THE EPICENTRE

In Bangalore, the bustling capital of the southern state of Karnataka, people drive shiny new cars, work in gleaming new buildings and carry mobile phones. Just a few hundred kilometres north, the residents are poorer than many in sub-Saharan Africa. In Bangalore, dubbed India’s Silicon Valley, the land is green, but here it is brown and dry. This is the home of one of India’s two AIDS hotspots.

“Someone’s got to wake up to the fact that there are two Karnatakas,” says Ashok Alexander, director of Avahan, the Bill & Melinda Gates Foundation’s AIDS programme in India. Driven by poverty and unemployment, women from northern towns such as Bijapur and Belgaum travel across the border to work as prostitutes in the richer cities in the adjoining Maharashtra state. When they return home, they bring the money they’ve earned — and HIV. On a map (right), the districts along this ‘AIDS corridor’ are immediately visible. “This is the epicentre of the whole Indian AIDS epidemic,” Alexander says.

He has discussed his theory with several people in the government. “We entirely agree with him because those pockets are surely high-prevalence,” says S. Y. Quraishi, director-general of the National AIDS Control Organization.

Yet until Avahan — meaning ‘call to action’ in Sanskrit — was launched in April 2003, Karnataka was largely ignored by AIDS groups. Most donor agencies ‘adopted’ other high-prevalence states: the US Agency for International Development earmarks its money for Tamil Nadu and Maharashtra, for instance, and Britain’s Department for International Development champions states such as Andhra Pradesh. Avahan has already spent more than US$17 million working with sex workers, truck drivers and drug users. It is also backing research on migration patterns in the corridor, large-scale surveys to measure behavioural changes and mathematical models that chart the epidemic’s course. “We’re going to be here as long as it takes to make an impact,” says Alexander.

A.M.

“The word HIV we keep quiet. If you start with HIV, they’ll run away,” Selvaraj explains. “That’s my last chance to talk to him so I should prepare to interact with him in such a way that he remembers.”

These truckers go home only once every few months. On the road, they have multiple sexual partners and often abuse drugs and alcohol. Many believe that if they don’t have sex they will build up garmi, a Hindi word meaning heat, and will go blind.

In recent years, they’ve become accustomed to being chased by volunteers with flipcharts and penis models in their pockets. Selvaraj works with the HOPE Foundation, which has counsellors and doctors at several stops along a 60-km stretch on the highway. But the message has not entirely got through. Believing that AIDS can only be transmitted by women, many truckers now have sex with ‘cleaners’, the young boys who travel with them. Homosexuality is illegal in India, so the government’s campaigns mostly neglect men who have sex with men.

These truckers have ample access to condoms, but many use the condoms to plug pipes in the trucks. According to a report by India’s comptroller and auditor-general, 75% of the 1.5 billion condoms made each year are used as sealants for leaky roofs, as lubricants and penis models in their pockets. Selvaraj adds, “We’re going for 100% condom promotion,” says health minister Anbumani Ramadoss. “Our job is giving them awareness. After that, if they don’t use it, what can we do?”

Apoorva Mandavilli is senior news editor of Nature Medicine.