

A Nation of Guinea Pigs

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There's a new outsourcing boom in South Asia - and a billion people are jockeying for the jobs. How India became the global hot spot for drug trials.

By Jennifer Kahn

The town of Sevagram in central India has long been known for three things: its heat, which is oppressive even by Indian standards; its snakes, which are abundant; and its ashram, a derelict and increasingly malarial retreat preserved as a tribute to Mohandas Gandhi, who lived here and was known for tenderly relocating the poisonous vipers that slithered into his shack.

Despite this intemperate setting, Sevagram's hospital has a good reputation. Though the power fails often, forcing medics to use the backlit screens of their cell phones for illumination, the standard of care is higher than at many of the country's public hospitals, and the facilities are comparatively plush. At the nearby government medical center in Nagpur, for instance, patients sometimes have to sleep on mattresses on the floor.

Last year, Sevagram began garnering even more cachet. A German pharmaceutical company called Boehringer Ingelheim, whose latest stroke-prevention drug was making its way through the clinical pipeline, approved the town's hospital as a trial site - one of 28 in India recruiting stroke victims to round out the company's 18,500-person study.

The drug regimen, known as Aggrenox, was being tested for its ability to forestall a second stroke. S. P. Kalantri, the doctor tapped to lead the trial in Sevagram, quickly grasped the offer's appeal. Patients in Sevagram are poor enough that the benefits of taking part in the study would amount to a health care windfall; among other things, Boehringer Ingelheim guaranteed participants two physicals during each of the three years that the trial would run. For each person enrolled, moreover, the hospital would receive 30,000 rupees (about \$665) - no small amount, given the puny budget of the center's stroke ward, a single room of eight pallet beds. Kalantri talked the matter over with the chair of the hospital's ethics committee, and the two concluded that the trial drug itself, with its possible side effects and limited efficacy, would provide little benefit to their patients. Then they went ahead and signed up.

When I arrive in Sevagram on a typically sweltering October afternoon, Kalantri is midway through a busy day. That morning, he attended to a farmer who had been bitten on the heel by a viper while sleeping, and then to a woman who had drunk a quart of insecticide in a suicide attempt. He also checked on his regular patients: a man with cerebral malaria, two women with unexplained fevers, and a stroke patient who had hemorrhaged. When I ask what treatment he gave to the stroke victim, he seems surprised. "Nothing," he says. "There's nothing we can do."

Though hemorrhagic strokes are untreatable - drugs can't undo the damage - Kalantri's response echoed a more persistent frustration: that patients are too poor to pay for medicine. Because of this, one of the alluring features of a clinical trial is that subjects are supplied with the test drug for free. And while the medication on offer isn't always a very useful one, there's still the chance that it will do some good.

This casual optimism contrasts sharply with the attitude in the West, where the number of patients willing to sign up for clinical trials is abysmally low. Just 3 percent of cancer patients opt to join trials, and the number of US patients who sign up for cardiac trials has plunged by half over the past five years.

Such reticence has created a problem for the pharmaceutical industry. Modern drug design may be a sophisticated enterprise, harnessing technology that didn't even exist a decade ago, but one part of the process remains the same: The only way to tell how well a medication really works is to feed it to a sick

person. This process, the human clinical trial, is the largest and creakiest part of the drugmaking machine - a mammoth lab experiment that succeeds by brute statistical force. To make it run, companies have to round up a large number of ailing people and then convince them to swallow an unproven remedy with uncertain side effects.

The experiment unfolds in three stages: Phase I, when a compound is safety-tested on a few dozen healthy people; Phase II, conducted on a slightly larger group of mildly ill subjects; and Phase III, which is the most extensive. Involving thousands of subjects and taking up to seven years to complete, Phase III trials are the make-or-break point for new medicines and, because of their size, the hardest to fill with patients. Exacerbating the problem is the fact that discoveries of rare side effects (including lethal ones, like strokes and heart attacks caused by the arthritis drug Vioxx) have pushed companies to conduct ever larger studies. In the 1980s, a new drug typically was tested on 1,300 volunteers in a total of 30 trials. By the mid-1990s, those numbers had swelled to 4,200 patients and 68 trials.

"Twenty years ago, drugs were dropping the cardiac mortality rate from 20 percent to 15 percent," says Dhiraj Narula, medical director of Quintiles ECG, a contract-research firm that organizes trials for major multinationals. "Today we're looking at drugs that will take you from 6 percent mortality to 5 percent. To prove an effect that subtle, in a way that's statistically robust, you need a lot of patients in your sample." One cardiac drug study was conducted on a whopping 41,000 subjects.

The result is a bottleneck that Narula argues is impeding the arrival of important cures. Herceptin - an exceptionally effective breast cancer drug - languished in trials for years because its maker, Genentech, reportedly couldn't recruit enough patients to test it.

Like many in the pharmaceutical industry, Narula believes that the solution to the slow pace of drug trials lies in outsourcing. As many as half of all clinical trials are already conducted in locations far from the pharmaceutical companies' home base, in countries like India, China, and Brazil. And many industry analysts expect the market to skyrocket, particularly as expanding libraries of genetic information increase the number of drugs coming out of the lab. The consulting firm McKinsey calculates that the market in India for outsourced trials will hit \$1.5 billion by 2010.

Enticed by numbers like these, developing countries have been scrambling to catch Big Pharma's eye - India most aggressively of all. Like high tech call centers and software farms, which were meant to transform India's computer industry by creating skilled workers and a stockpile of modern equipment, drug trial outsourcing is seen as the fast route to economic and scientific growth - a money train that the country can't afford to miss. With this in mind, the government is working to advertise India's most pharmacologically appealing qualities, notably its doctors (English-speaking and educated abroad) and its vast number of ailing patients - 32 million diabetics alone. Many of these patients are also, in the delicate parlance of the drug world, "treatment naive," meaning they've never taken any medication for their illnesses. This is a perk for trial managers, because it lowers the risk of unforeseen drug interactions and avoids the troublesome process of weaning patients off one medication and onto another.

Last year, the government took a more controversial step, amending a long-standing law that limited the kind of trials that foreign pharmaceutical companies could conduct. That law allowed companies to test drugs on Indian patients only after the drugs had been proven safe in trials conducted in the country of origin. In January, the government threw out that constraint. India, the brilliant hub of outsourced labor, was positioning itself in a newly lucrative role: guinea pig to the world.

The headquarters of Sevagram's Aggrenox trial, located around the corner from the hospital's intensive care unit, is low on frills. A drooling corner sink and two elderly computers list against the water-stained walls, under the benevolent gaze of a small plastic bust of Gandhi. A handful of scientific papers have been tacked to the wall, where they hang unstirred by a sluggish fan. Since recruitment for the trial began in January 2005, Kalantri has signed up 44 stroke victims, a quarter of the number that have come through the hospital.

Nonetheless, Kalantri is uneasy about his clinical success. "Patients here are very passive," he reflects. "They will almost never question their doctor." Indeed, one woman who joined the trial six months ago sits patiently for more than an hour while Kalantri translates my questions, before revealing that she is suffering from aches and fever that are likely malaria. Such deference is hard to imagine in US patients - a querulous lot - and it makes Kalantri's position tricky. "Nine out of 10 times," he says, "the patient will just ask me to make the decision about the trial for him. So what role do I play? Am I a physician, concentrating on what's best for the patient? Or am I a researcher interested in recruiting patients? I try to balance the two sides, but ..." He shrugs. "It's a dichotomy."

Kalantri began worrying about such matters not long after he started recruiting patients for Boehringer Ingelheim. The previous year, he had overseen a trial for Reviparin, an anticlotting drug that improves the health of one out of 65 cardiac patients within 30 days of a heart attack. The trial was enormous: Nearly 16,000 patients participated, half of them from India. When the trial ended, however, Kalantri wondered whether he had served his patients well by enrolling them. At 800 rupees a day, the drug they had taken was too expensive for any of them to afford. Plus, even when it worked, it showed results for just a month. Such a minute and costly improvement might make sense in the US, Kalantri felt, but was it really the kind of medication that poor Indians should be testing? "The biggest problems around here are snakebite and insecticide poisoning," he points out. "We could really use a trial for one of those."

Kalantri is in a good position to observe such discrepancies. He grew up in the neighboring town of Wardha, 15 minutes away by auto-rickshaw, and got his training at the local medical college in Nagpur - a city whose main claim to fame is a survey plaque declaring it to be India's geographical center. He is a slight man, with a philosophical and conscientious manner. His wife is a database administrator for the hospital in Sevagram, and last year the older of their two children started attending medical school there. Although Kalantri could probably work elsewhere - in 2004, he did a stint at UC Berkeley, working on his master's in public health and collaborating on a tuberculosis study that was published in *The Journal of the American Medical Association* - he remains attached to the rural hospital he joined 20 years ago. "I found my peace of mind here," he says.

Initially, Kalantri says, he was excited by the idea of bringing clinical trials to Sevagram and liked the prospect of turning his hospital into a research center. "Drug trials can teach residents proper record-keeping and help them understand how to associate clinical care with research," he notes. When I first called him, shortly after a record rainy season, he mentioned that the emergency ward contained a number of patients with a mysterious fever - one that epidemiological tests had been unable to identify. "It would be good to study it," Kalantri murmured, sounding a bit regretful. "Maybe we will, one day."

Bringing trials to India, moreover, struck him as medically important. A *Nature Genetics* article had recently surveyed 29 drugs whose efficacy and side effects varied in different racial or ethnic populations. Perversely, testing drugs exclusively on Americans and western Europeans could almost seem colonial.

Little by little, however, Kalantri began to see the problematic side of outsourced trials. "When I try to explain that a drug is experimental, that it might not work, the understanding is not there," he observes. "One woman said to me, 'What do you mean, the drug might not work? All drugs work!'"

Poorly paid doctors can also find the financial rewards of a trial hard to resist - particularly since pharma companies reward high enrollments with prizes like vacations to Hawaii and Europe. "A lot of private hospital doctors have suddenly become 'researchers,'" Kalantri notes. "They will enroll almost anybody and recruit for almost any trial, whether or not it helps the patient." And while the money earned from a trial in Sevagram goes to the hospital, elsewhere it may be paid to the doctor. "A lot goes into personal bank accounts," he says.

Naïveté and corruption are hardly unique to India, of course. They're the early story of almost any developing industry, when regulation is still too flimsy to check the horses of rapid progress. Compared to a country like China, for instance, India is alert to the potential for exploitation and has made at least some effort to safeguard its citizens. Programs to train clinicians in World Health Organization-standard Good

Clinical Practice - a set of international rules covering patient rights and data management - have sprung up around the country. In addition, all trials must ostensibly be cleared by a local review board that includes one doctor, one lawyer, and one pharmacist, as well as a housewife and a social worker.

In practice, however, policing trials is not easy. The enforcement staff of the Drugs Controller General of India - the equivalent of the US Federal Drug Administration - consists of just three pharmacists. And the country has little history of keeping medical care independent of the pharmaceutical business. The largest cardiac hospital in India, Escorts Heart Institute and Research Centre, is a division of the massive Indian pharmco Ranbaxy.

"Are patients here more vulnerable?" asks Brijesh Regal, CEO of the New Delhi-based firm Apothecaries, which runs clinical trials for pharmaceutical companies. "Obviously. They're poor. They're illiterate." Nonetheless, he argues, most of the problems can be attributed to the growing pains of a new industry. He points to the thalidomide fiasco in the 1950s - women who were given the drug for morning sickness delivered children with severe birth defects - as evidence that every developing industry has problems. "Why are we so concerned about India?" he asks. "If problems happened everywhere else, they will happen here. We are a massive country without a lot of regulatory infrastructure."

Regal's willingness to accept collateral damage may seem chilling, but it has some historical precedent. The path of medical progress is strewn with cases of questionable ethics, desperate practices, and misguided experimentalism, if not outright exploitation. And since patients with the fewest options are invariably the ones most likely to try (or be forcibly volunteered for) risky new treatments, be it an artificial heart, an unproven pill, or a radical lobotomy, they're also the ones who bear the brunt of medicine's experimental nature. In this light, outsourcing trials to a country where decent medical care is scarce, and medication scarcer, is just the globalization of an old equation.

Kalantri, meanwhile, finds himself stuck in the uncomfortable role of gatekeeper. "Every week, I get a call: 'Do you want to participate in this trial?'" he says. So far, he has turned down one anti-osteoporosis trial and another for a drug that might improve patient survival after a heart attack. He declined, he explains, because the studies "don't make sense for India." Finding better treatments for osteoporosis and high cholesterol is important, he adds. "But these are diseases that will cause problems at 40 or 50. Infectious diseases like malaria and filariasis kill at 20, and they're much more common here."

Kalantri is also troubled by what he sees as skewed trial demographics. "Ninety percent of patients being recruited in India are poor," he says. "That's the reality. Trials enroll very few patients who are rich, literate, and capable of asking awkward questions."

But even as Kalantri has grown more selective, other Indian doctors are moving in the opposite direction. And at his own hospital, Kalantri's pickiness has been a subject of debate. "Some of my colleagues are not exactly happy with these decisions," he sighs. "The extra money could be used to build the department."

Finding a dollar amount that compensates medical centers properly - covering costs like blood tests and the extra time a doctor must spend with study patients, without amounting to a bribe - is tricky, Kalantri says. He confesses that he has turned down trials because they paid too little. Nonetheless, when a representative from Boehringer Ingelheim visited to check up on the paperwork, Kalantri felt compelled to mention that the amount the company was offering per patient seemed high. The rep looked at him in surprise. "You're the first person to say that," she said, giving Kalantri a puzzled smile. "Everyone else has asked for more."