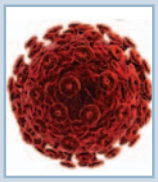
p112 Up in smoke: Cheap biomass fuels are claiming lives of poor women and children.

p113 Brainy benefactor: Vikram Kumar has set up a shop to solve public health problems.



p116 HIV's lair: Damage in the gut reflects the real extent of AIDS's toll.

Reformed US malaria program garners critics' approval

It's been almost two years since the US Congress, spurred by reports that the country's malaria aid programs were hemorrhaging money, took the responsible agency to task for poor accounting and outsize payments to consultants.

The administration seems to have got the message.

US malaria programs now post their budget and contracts on public websites, have shifted more money to spraying insecticides, including DDT, for mosquito control (*Nat. Med.* **12**, 870–871; 2006), and spend less money on consultants and meetings, according to a December report by the advocacy group Africa Fighting Malaria (AFM), which was among those who excoriated the programs.

"Things are 100-fold better than they were," says Amir Attaran, professor of population health and law at the University of Ottawa, who triggered the congressional scrutiny with several articles in 2004 criticizing the United States Agency for International Development (USAID), which runs the malaria programs. Among his charges were that the agency could not provide detailed audits of its malaria spending (*Nature* **430**, 932–933; 2004).

In May 2005, an AFM report concluded that USAID was spending less than 10% of its malaria funding on supplies such as drugs, insecticidal bed nets and sprays. The rest of the money went to other costs such as meetings and consultants' fees.

"We didn't particularly like the news," says Admiral Tim Ziemer, who has been chief of USAID's malaria operations since last summer, "but it was accurate."

Responding to the growing scrutiny, the administration in June 2005 launched the $1.2 billion five-year President's Malaria Initiative, which is administered through USAID. The initiative last year spent about half of its money on drugs, bed nets and sprays.

Funding for the initiative is projected to be $300 million per year from 2008 to 2010—compared with $80 million in 2004 and $14 million in 1998. The president has asked Congress for $135 million for 2007, but it is unclear whether that amount is likely to be approved in a time of tight budgets.

Since the initiative is so new, evidence of its impact is still being gathered. But AFM says USAID has improved its ability to tally incidence of disease and death.

The agency is also working better with partners such as the Global Fund to Fight AIDS, Malaria and Tuberculosis. "In the past this is not something we had seen a lot of," says Philip Coticelli, an AFM researcher.

Coticelli and others are still concerned that the agency is using many of the same contractors as before. Attaran notes that some contracts on the initiative's website display erased information—including total costs and cost ceilings. "There is a sham of transparency here, it's not actual," says Attaran. "There are serious problems that remain."

USAID officials say the agency is trying to strike a balance between transparency and proprietary information.

"The [initiative] is not interested in sugar-coated bureaucracy," says Ziemer. "We want to be held accountable."

Charlotte Schubert, Washington DC

Associated Press

Pest control: The US malaria program is spending up to half its budget on drugs, bed nets and spraying of pesticides such as DDT.

Supplement makers face bitter pill

The last time US Democrats controlled Congress, in 1994, dietary supplement makers received a huge windfall: a new law that gave them the right to make unproven health claims about their products.

This time around, things don't look quite so rosy for the industry, which has grown from a $9.5 billion enterprise in 1994 to a $22 billion behemoth.

"We will take a hard look at dietary supplements," Democratic congressman John Dingell, new chairman of the House Energy and Commerce Committee, told reporters the day after the November elections. "You might even find that the Department of Justice will be looking into possible criminal sanctions."

The Dietary Supplement and Non-prescription Drug Consumer Protection Act, signed into law in December, and largely supported by the industry, requires companies to report adverse reactions to the Food and Drug Administration (FDA), but puts the onus on the agency to prove that a supplement is unsafe.

Since 2003, following reports of deaths related to ephedra (*Nat. Med.* 9, 634–635; 2003), Dingell has tried to push through another bill that would significantly boost the FDA's authority to investigate supplements, even when the agency has not received reports from the companies of bad reactions.

Supplement makers have no incentive to bring dangerous products to market, says Steven Mister, president of the Council for Responsible Nutrition in Washington, a lobbying group for some 80 supplement firms. "Somebody who is in this for the long run is going to take care of their consumers."

Meredith Wadman, Washington DC

Tied up in red tape, European trials shut down

The chemotherapy drug doxorubicin has been used to treat soft-tissue cancers in children for more than 20 years, but doctors don't know the most effective dose, nor how it interacts with other drugs.

In 2005, European researchers set out to find these answers in a large, multi-center trial.

Two years on, fewer than half of the 600 participants needed have been recruited. Only 2 of the 16 countries originally involved—Italy and France—began on time. Denmark has yet to start, and Poland, Austria, Sweden and Germany—the last expected to provide 25% of study subjects—dropped out. Trial coordinators canceled plans to analyze data part way through the study. The trial's 2010 end date is likely to be pushed back by at least two years.

Scientists say the study is merely the latest victim of the Clinical Trials Directive, implemented by the European Union in May 2004 to make trials safer and more consistent. The directive, aimed largely at holding pharmaceutical companies to higher standards, has tied up academic clinical research, particularly large trials, with redundant paperwork, liability tangles and unending bureaucracy.

"The directive has caused a huge headache," says Kathy Pritchard-Jones, European branch president of the International Society of Paediatric Oncology. "We're starting to see holes in the research portfolio."

The cost of academic cancer trials has doubled since 2004, according to Cancer Research UK, the country's largest sponsor of academic cancer research. The European Organization for the Research and Treatment of Cancer estimates that expenses have risen by 85% and says the number of trials it supports has dropped by 63%. The Save European Research campaign, which represents more than 3,000 scientists, says academic drug trials have dropped by 70% in Ireland and 25% in Sweden. The number of Finnish academic drug trials shrunk by 75%.

TRIAL AND ERROR

The European Clinical Trials Directive has created bureaucratic nightmares and is shutting down trials. Since the directive's launch:

Increase in the cost of academic cancer trials in the UK	200%
Drop in academic drug trials in Finland	75%
Drop in academic trial submissions in Ireland	70%
Increase in the cost of trials supported by EORTC	85%
New trials supported in 2004 by the group	19
New trials supported in 2005 by the group	7

Sources: Cancer Research UK; *Brit. Med. J.*; EORTC

Because the directive is technically not law, each of the European Union's 27 member countries was free to set it up differently, creating vast differences in rules across countries.

"In France, they told me that we couldn't include ethnic groups as a category in our database," says Gianni Bisogno, a pediatric oncologist at the Hospital of Padova in Italy. "We had to change the database, which meant more time, more money."

More problematic than those logistical details, researchers say, is the patchwork of requirements for reporting adverse events.

In Germany, for instance, investigators must file a report on every unexpected adverse event in each of a trial's centers, as well as relevant information produced by any researcher in the world who studies the same treatment.

"They're getting overwhelmed with the amount of paper they've got to sift through," says Pritchard-Jones. She adds that truly important adverse events may get overlooked in the pile.

The biggest bottleneck, researchers say, is the directive's requirement that each trial have a single sponsor assume full legal and financial liability.

"There are not many institutions willing to take responsibility," says Mariana Resnicoff, coordinator of the European Science Foundation's collaborative research program.

The European Commission is studying how to fix the directive, spokesman Ton van Lierop said in an email. "If not properly addressed, [the problems] may impact negatively in the fulfillment of the directive."

Brandon Keim, New York

Ambitious scheme for developing world trials in 'big trouble'

When the European and Developing Countries Clinical Trials Programme (EDCTP) was formed in 2003, some public health experts worried that the pan-European scheme would conflict with national research programs. Others wondered whether its emphasis on AIDS, malaria and tuberculosis would cause other diseases to be neglected.

Four years later, with the program's fourth executive director set to take office, those fears seem naively optimistic.

With a €600 million budget, the EDCTP is the largest European sponsor of developing-world drug trials. But it has thus far funded only eight trials. Staff turnover, grant squabbles and communications breakdowns have plagued the program, and its potential remains largely unfulfilled.

"The EDCTP is certainly in big trouble," says Mario Raviglione, director of the World Health Organization's Stop TB partnership.

Although €87 million was reserved for future grant calls, just €24 million has been awarded so far. Complaints over the program's first round of grants led in September 2004 to the ouster of its then-executive director, Piero Olliaro. The next call for grants was released only in early 2006. By October, Odile Leroy, the third director in as many years, had stepped down to head the European Malaria Vaccine Initiative.

The board in January approved Charles Mgone, the Tanzanian-born head of the program's African office as its next director.

The high staff turnover and organizational bureaucracy has left some would-be partners, including Raviglione, unsure of whom to contact on important matters. No one from the program has ever contacted Stop TB, Raviglione adds. "I simply have no idea what they're doing, and when I ask around, not many people know what's going on over there," he says.

Cynthia Naus, the program's operations manager, says staff have worked with the WHO on non-tuberculosis projects. The director of the WHO's Tropical Diseases Program is also an observer on the main strategizing group, she adds.

"The EDCTP has had a slow start, but it was also an organization that was literally built from scratch," Naus says. "We do realize the urgency."

Brandon Keim, New York

Australia set to test insulin 'vaccine' for juvenile diabetes

A 'vaccine-like' approach to juvenile diabetes, set to be tested in a clinical trial in Australia, aims to test whether delivering insulin through the nose can keep the immune system from attacking the body's own cells.

Vaccines prime the immune system to attack invaders and protect the body. But in type 1 diabetes, it is the T cells that attack and destroy insulin-secreting beta cells in the pancreas.

In a phase 2 trial announced in December, Australian researchers are testing whether nasal insulin delivered to people at risk of type 1 diabetes can prevent the disease by training their immune systems to tolerate beta cells.

Edwin Gale, head of the diabetes research unit at the University of Bristol, says although it is too early to speculate on whether the approach can prevent type 1 diabetes, it could add to scientists' understanding of immune tolerance.

Calling the approach 'vaccine-like' has provoked some skepticism from experts who say vaccinating against an autoimmune disease is inherently contradictory.

Warwick Anderson, chief executive of Australia's National Health and Medical Research Council, which co-funded the trial, says the term is a bit of a misnomer. "That word 'vaccine' stuck early on, 'immune regulation' would be better."

Insulin administered via the nose or mouth stimulates the immune system via the mucosal lining but is not absorbed further and does not affect blood glucose levels. A phase 1 trial completed in 2004 found immune responses similar to those seen in mouse studies.

A significant increase in antibodies to insulin accompanied a decrease in T-cell response, the first demonstration of this effect in humans. Project leader Len Harrison, of the Walter and Eliza Hall Institute in Melbourne, says the approach is based on the phenomenon of mucosal tolerance first reported in the 1940s.

"It seems paradoxical because insulin antibodies are a marker for the disease, but there is no evidence that antibodies themselves cause damage to beta cells," he says. The more important thing, he adds, is that the method suppresses the immune response to insulin.

In a separate project, Matthias von Herrath is investigating whether those who have recently contracted the disease would benefit from a combination of nasal insulin and drugs to suppress the immune system.

"Our studies have shown that such combo-therapies are much more effective," says von Herrath, head of the Immune Regulation Lab at the La Jolla Institute for Allergy and Immunology.

Previous attempts to show mucosal tolerance in people with type 1 diabetes have all failed (*Diabetes Care* **27**, 2348–2355; 2004). But those studies involved individuals with end-stage disease who received oral insulin.

Delivering insulin through the nose would prevent it from degrading before it reaches the mucosa, Harrison says. The phase 1 trial suggested that although the treatment does not eliminate the T cells that destroy beta cells, it might enhance the T cells that help make antibodies. "You would have a mixture, it's a balance between the good guys and the bad guys," Harrison says.

At least 13,200 relatives of people with type 1 diabetes will be screened in order to identify 264 participants at high risk. Results are expected in seven years.

Simon Grose, Canberra

US proposal to expand access to untested drugs draws fire

Should those who are sick or dying and have exhausted all other options be able to try drugs that haven't yet been approved? The US Food and Drug Administration (FDA) seems to think so and in December proposed a controversial scheme to help people get the drugs they need.

The move could cause chaos, jeopardizing drug development and exposing scores of people to unsafe drugs, experts caution.

The proposal is controversial not least because it allows people to try drugs in early stages of testing—in rare circumstances, even those that have never been studied in humans. Some of these might later prove to cause nasty side effects or even death, critics note.

The most common way for an individual to get an experimental drug is to enroll in a clinical trial. Not everyone qualifies for these studies, however, and some participants receive a placebo rather than the drug.

The FDA has for decades allowed people dying of certain "life-threatening" diseases, such as AIDS and cancer, to try experimental drugs outside of clinical trials. But the process of applying on the grounds of 'compassionate use' is convoluted, sometimes requiring inside contacts at a company or at the FDA.

Hidden dangers: New rules would allow those with serious illnesses to take unapproved drugs.

For example, the rules also allowed those with a "serious" illness, such as depression and rheumatoid arthritis, to apply for experimental drugs, but the definition of serious was buried in a separate set of regulations.

The new rules clarify those ambiguities, spelling out who is eligible for these drugs, how to request them and how much companies can charge for them. The proposal is under a 90-day review that ends in March.

"We believe these rules, when finalized, will help reach out to other populations," says Rachel Behrman, deputy director of the FDA's office of medical policy. "We will review every request."

As people learn more about these rules, however, the agency might find itself flooded with requests for investigational drugs for anything from depression to cancer. Drug makers, which have traditionally resisted supplying experimental drugs because of liability issues, might also succumb to the demand. The proposed rules might in part be a response to a lawsuit brought by the Virginia-based advocacy group Abigail Alliance (*Nat. Med.* 12, 596, 2006).

"Making this a little more accessible may cause the well-informed patients to be more demanding," says Richard Kingham, a partner at the law firm Covington and Burling. "And history shows that if there's pressure, a company will consider supplying the drug."

Most antidepressants work for only about half of those who take them. If companies release those drugs, it could paint a misleading picture of the drug's safety and efficacy. It could also take away incentives for individuals to enroll in clinical trials.

Expanding access to experimental drugs "could be a disaster for the drug approval process," says Jerry Menikoff, a health law expert at the University of Kansas. "The only reason some people enroll in studies is because they need the drug."

Emily Waltz, New York

Biomass fuels blamed for premature deaths in rural settings

Pollution is seen mostly as an urban problem, with mega cities spewing soot and fumes into the air. Twigs, leaves, dung and the countryside hardly fit that picture.

In millions of homes across rural Asia, Africa and Latin America, however, indoor air pollution caused by burning biomass and coal over primitive stoves is deadlier than outdoor pollution.

Indoor pollution causes roughly 1.6 million premature deaths each year, twice those caused by outdoor pollution, according to the World Health Organization. "Insidiously, it targets women and young children in the poorest households," says Kirk Smith, professor of public health at the University of California, Berkeley.

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Burning problem: Popular in rural households, cheap biomass fuels cause deadly indoor pollution.

An estimated 3 billion people use biomass fuels to cook food and heat their homes worldwide, mainly because they cannot afford any other fuel. Biomass fuels account for nearly a tenth of the global energy consumed and their numbers are expected to rise substantially by 2030.

Although indoor pollution is ranked eighth as a risk factor for the global burden of disease by the World Health Organization (WHO), it ranks fourth in developing countries and third in India for the national disease burden.

Pneumonia in children and chronic lung disease in women are the most severe and common effects. In China, the high incidence of lung cancer in women is linked to open coal stoves, says Smith. Tuberculosis, heart disease, blindness, cataract, immune and metabolic changes and still births also result.

The fuels do not burn completely, emitting polluting gases such as carbon monoxide, nitrogen dioxide, sulfur dioxide, the cancer-causing chemical benzopyrene and fine particles less than 10 microns in diameter that damage lung tissues.

A biomass Indian stove, for example, converts between 6% and 20% of the carbon into pollutants. Poor ventilation in homes traps the gases inside, compounding the problem.

Biomass fuels account for 80% of domestic energy consumption. "With the Indian government's ban on cutting trees for fuel wood, many are using crop residues and dung that have worse combustion efficiencies than wood," says Twisha Lahiri, assistant director of Chittaranjan National Cancer Institute in Kolkata.

Lahiri's team has found evidence of genetic damage and, more recently, of blood platelets sticking together—a risk factor for blood clots—in women with chronic exposure to biomass smoke (*Hum. Exp. Toxicol.* **25**, 627–635; 2006). The disease pattern is the same in outdoor and indoor pollution, but the impact is more severe in biomass users as they are more exposed to the fumes within their homes.

Preliminary data from a trial on 530 households in Guatemala shows that young children in households cooking with open wood fires also contract more severe forms of pneumonia, Smith reported at a December workshop in Indonesia on better air quality.

Fields where biomass wastes are burnt are equally damaging. For example, Brazil burns about 20 tons of sugar cane waste in fields each year. A Sao Paolo University study has found that the increase in fine polluting particles during the burning period correlates with a 21% rise in respiratory illnesses in children and a 31% increase in the elderly (*Env. Health Persp.* **114**, 725-729; 2006).

Although evidence of the dangers is mounting, there is overall a lack of research interest in the subject, says Smith. "It took 17 years to get international funding for a health study after the first measurable evidence from India in 1981," he says. "Unfortunately poor people in rural areas do not have much clout."

T.V. Padma, New Delhi

British scientists find patent loophole

Two British researchers say they have found a way to produce low-cost versions of expensive pharmaceuticals without breaking patent laws.

Sunil Shaunak and Steve Brocchini call their products "ethical pharmaceuticals."

Their first target is a naturally occurring molecule called interferon, which is used to treat hepatitis C. Commercial interferon has a coat of sugar molecules that reduces side effects and helps it last longer in the body. It is safe and effective, but also expensive.

In the UK, a full course of treatment costs around £7,000, well beyond the means of most people in the developing world. Hepatitis C affects 200 million people and kills about half a million people each year.

The researchers attached sugar molecules to a different part of interferon, creating a configuration that may be novel enough to evade existing patents.

If it passes regulatory hurdles—and legal challenges—the compound would then be made affordable in the developing world. Patents on the process, along with the resulting interferon formulation, are held by PolyTherics Ltd., a company founded in 2001 by the researchers. Shantha Biotech, based in Hyderabad, India, has agreed to produce the drug, and the Indian government is set to conduct clinical trials.

Shaunak says other researchers should follow this example by reformulating other drugs. They have also partnered with the Drugs for Neglected Diseases Initiative to alter a leishmaniasis treatment. Drugs created by this method will need to be approved by regulatory agencies.

Pharmaceutical companies Roche and Schering-Plough, which hold patents on sugar-coated interferon, declined to comment. But Frederick Abbott, a Florida State University law professor and intellectual property expert, says the patents are sure to be contested.

"Are scientists morally and ethically justified in trying to develop workarounds to the patent system to provide treatment to more people? Absolutely," says Abbott. "But one shouldn't assume that industry is just going to accept that."

Brandon Keim, New York

Vikram Kumar

With a dash of tech savvy and a dose of medical wisdom, Vikram Kumar is trying to solve intractable problems in public health—and all at the ripe old age of 30.

In rural Zambia, people are often on the move, changing homes, schools and clinics with every move. Their medical records are rarely, if ever, maintained by hospitals.

But since last year, 60,000 HIV-positive Zambians in Lusaka district have carried their entire medical histories on plastic 'smart cards'—like those used at gas stations or office cafeterias in the US or Europe. When a doctor swipes the card at a clinic's computer, a program pulls up the person's entire medical record, helping the doctor decide on the best course of treatment. The transaction is then recorded in a central database that can later be used to track outcomes and order new drugs.

This creative system, dubbed SmartCare, was designed in consultation with Zambia's Ministry of Health and the US Centers for Disease Control and Prevention (CDC) by Dimagi, a tiny Boston-based informatics company.

A clinician, programmer, entrepreneur and do-gooder, Vikram Kumar has turned Dimagi into a one-stop technical shop for public health experts who use data management to save lives—and this before his academic career has even begun.

Just 30, Kumar is finishing a residency in clinical pathology at Boston's Brigham and Women's Hospital, where he is trying to combine patient records with the hospital's architectural plans in order to track the spread of hospital-acquired infections.

"He has a much broader appreciation than most people for the texture of human life," says Sandy Pentland, chief of the Massachusetts Institute of Technology (MIT)'s Media Lab. "Partly it comes from his Indian-American perspective, but also he's done work on rural health care in Africa and India while being at a high-tech medical institution."

Born in Buffalo, New York, Kumar moved to New Delhi at age ten. Hoping to bring his children closer to their Indian roots, his father had abandoned a neurosurgery practice and instead took on sundry projects, from selling leather to helping start a hospital. That spirit of adventure inspired Kumar, as did the *swamis* who often stayed with his family.

"You become more thoughtful, living with people who have renounced everything," says Kumar. "They are constantly pursuing knowledge, bettering themselves, giving themselves. My father and mother are the same. That gave me a passion to do this work."

Kumar learned to write code at the prestigious Indian Institute of Technology in New Delhi, where he spent a year studying textile engineering. Anxious to pursue more philanthropic ends, he transferred to Columbia University in 1995 and began studying medicine, business and engineering. In 1999, he enrolled in Harvard University's Health Sciences and Technology program, offered jointly with MIT. It was there that he met Dimagi co-founders Tarjei Mikkelsen, a medical software engineer, and Vishwanath Anantraman, who had been a physician in rural India.

Around this time Kumar also attended a public health conference where speakers discussed the benefits of wiring Africa for the Internet, but didn't address where the money would come from or whether people could benefit more quickly from simpler systems.

"The idea that you needed a huge infrastructure that didn't yet exist struck me as excessive," says Kumar, who figured that small-scale interventions using already-available products made more sense.

At the media lab, he developed DiaBetNet, a guessing game designed to help children with type 1 diabetes with the arduous task of tracking their diets and blood sugar. Named by *Business Week* magazine as one of the top ten designs of the 1990s, DiaBetNet never went beyond academic use, but embodied a focus on individual user experience that has become Kumar's signature.

On a wet winter day in Boston, Kumar is the picture of a techno-visionary humanitarian, wearing a lime-green sweater and red-framed glasses and jumping wildly from topic to topic, waving his hands excitedly. But he is disarmingly modest about the limits of his technology. "If it becomes clear the problem is about something else than the software we can write, we won't even do it," he says.

Kumar is quick to admit to his earlier mistakes, when Dimagi concentrated more on user-friendly technology than on making it sustainable in a low-tech environment. The company's first program, which gave handheld computers to nurses in rural India, folded after the Indian government cut its funding and the media lab's Asian office closed. A project for ensuring the confidentiality of HIV tests in South Africa failed because people who took the tests didn't want to know the results.

But when a Fortune 500 executive dismissed Dimagi as yet another fly-by-night graduate school project, Kumar and his colleagues came back to the company with renewed vigor. "There's no better way to get a guy like me to do something than to tell him he can't do it," Kumar says.

Kumar has cut back on writing code to concentrate on negotiating grants and finding partners with long-term plans and local expertise.

"Initially they were working in a high-tech, let's-go-in-and-try kind of way," says Hamish Fraser, director of informatics and telemedicine at Partners in Health, a Boston-based nonprofit that provides developing world health care. "Now they're developing long-term relationships, as in Zambia."

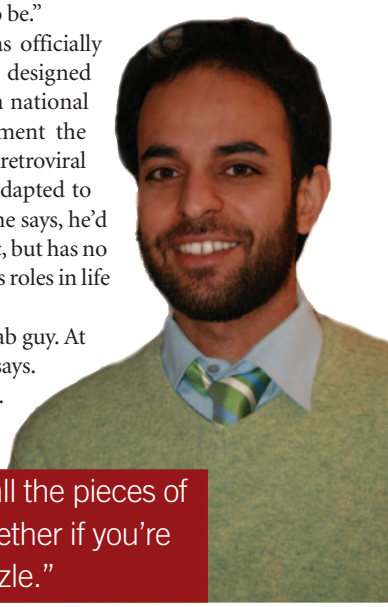
One of those relationships is with Stephen Rahaim, a program officer at the Program for Appropriate Technology in Health, a Seattle-based nonprofit health organization. After meeting Kumar over lunch, Rahaim immediately agreed to partner with Dimagi on an application to implement the US Agency for International Development's AIDS programs.

"It was a quick lunch, too," says Rahaim, who added that he usually takes months to negotiate such partnerships. "He's very open and engaging, speaks with a huge smile, and doesn't come with any assumptions about how grandiose the solution needs to be."

In Zambia, the Ministry of Health has officially adopted the record-keeping framework designed by Dimagi to accompany SmartCare as a national standard. The ministry plans to implement the program in every clinic that distributes antiretroviral drugs. Kumar hopes the system will be adapted to other countries and diseases. Eventually, he says, he'd like to open a personalized medicine clinic, but has no intention of leaving Dimagi or defining his roles in life more narrowly.

"At the medical school, I'm the media lab guy. At the media lab, I'm the medical guy," he says. "I feel that I need to be slightly outside. You can't fit all the pieces of the puzzle together if you're inside the puzzle."

Brandon Keim, New York



"You can't fit all the pieces of the puzzle together if you're inside the puzzle."

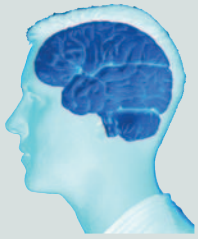
Timeline of events *...a brief history of the important news stories this month*

16 Dec

Women who receive high doses of hormones for *in vitro* fertilization are more likely to produce genetically damaged embryos, UK researchers report.

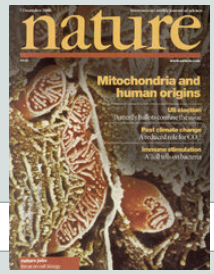
21 Dec

A specialized PET scan can detect deposits of amyloid and tau proteins, associated with Alzheimer disease, before symptoms emerge, US researchers say (*N. Engl. J. Med.* **355**, 2652–2663).



21 Dec

Citing a lack of participation by the scientific community, the journal *Nature* ends a peer review experiment in which accepted papers were posted for comment online before being published.



4 Jan

Margaret Chan officially begins her directorship of the World Health Organization—the highest UN office ever held by a Chinese national—promising to renew battles against avian influenza, malaria and polio.

1 Jan

Venezuela approves a new law requiring companies with revenues over $1.5 million to donate between 0.5% and 2% of their earnings to scientific research.

31 Dec

Scientists engineer healthy cows lacking the PrP^C prion protein, which causes mad cow disease when misfolded (*Nat. Biotechnol.* doi:10.1038/nbt1271).

28 Dec

Meat and milk from cloned animals win preliminary approval from the FDA, which says they can't be distinguished from traditionally produced animal products.

4 Jan

The US FDA approved only 17 drugs in 2006, the lowest number in a decade, and each drug cost an average of $1.5 billion to develop, says a study from Tufts University's Center for the Study of Drug Development.

4 Jan

Pergolide and cabergoline, two once-popular Parkinson disease treatments suspected of causing heart problems, trigger heart valve defects in up to a quarter of the people who take them, German and Italian scientists report (*N. Engl. J. Med.* **356**, 29–39, *N. Engl. J. Med* **356**, 39–46).

7 Jan

A new test can identify drug-resistant HIV strains before they become established in the body, and could help doctors determine which drugs are effective (*Nat. Meth.* doi:10.1038/nmeth995).

15 Jan

An ethics board of The New York Downtown Hospital conditionally approves experimental uterus transplants for would-be mothers whose wombs are defective or removed.

12 Jan

Population migration, prostitution, extramarital sex and rising health care costs have fueled a dramatic resurgence of syphilis in China, researchers warn (*Lancet* **369**, 132–138).

11 Jan

Viral resistance caused by a single large dose of nevirapine—a common method of preventing mother-to-unborn-child HIV transmission in the developing world—diminishes over time, and the drug can again be safely taken six months after initial treatment, US scientists report (*N. Engl. J. Med.* **356,** 135–147).

16 Jan

Home to more HIV-infected individuals than any other country, India proposes to spend $2.6 billion on its epidemic, a fivefold increase over its current investment.

17 Jan

The US FDA reprimands a Las Vegas doctor for not seeking federal approval before implanting at least 16 people with improperly harvested, tested and stored adult stem cells.

17 Jan

Of 71 products approved between 2000 and 2005 by both the US FDA and the European Medicines Agency, the FDA approved 52 about a year faster on average.

17 Jan

Two Egyptian family members are found to carry the first strain of H5N1 avian influenza that is resistant to the antiviral drug Tamiflu, the World Health Organization reports.

22 Dec

Trey Sunderland, the NIH researcher who received $300,000 in illicit payments from Pfizer, is sentenced to 400 hours of community service and ordered to forfeit the money.

22 Dec

Developing world researchers who partner with European scientists or institutions are eligible for the first time to apply for funds under the first calls for proposals for FP7, the European Union's €54 billion scientific research budget.

23 Dec

The US FDA followed only 72% of its advisory committees' recommendations between 2000 and 2004, and only one-quarter of drugs approved in the last six years were evaluated by an advisory panel, the Washington DC-based nonprofit group Public Citizen reports (*Lancet* **368**, 2210).

27 Dec

People over 50 who take heartburn medications for more than one year are more likely to break their hips, perhaps because the widely used drugs prevent their bodies from absorbing calcium, UK scientists report (*JAMA* **296**, 2947-2953).

26 Dec

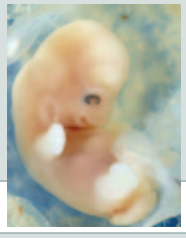
US President Bush's $15 billion program to fight AIDS in the developing world has failed to keep accurate records of expenses and activities, making it hard to assess whether the program works, according to a report from the US Agency for International Development.

24 Dec

Alleging racial discrimination, James Sherley, an African-American Massachusetts Institute of Technology stem cell researcher, vows to go on a hunger strike if not granted tenure.

7 Jan

Stem cells found in amniotic fluid are not only as versatile as embryonic stem cells and easier to maintain, but can be removed during routine prenatal testing without damaging the fetus, US scientists announce (*Nat. Biotechnol.* **25**, 100–106).



9 Jan

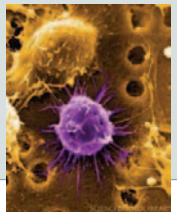
Milk proteins cancel the cardiovascular benefits of black tea by blocking the production of nitric oxide, which relaxes blood vessels, German scientists say (*Eur. Heart J.* doi:10.1093/eurheartj/ehl442).

9 Jan

US federal funds for stem cell research are sufficient and advances in adult stem cell techniques will soon render research on embryonic cells unnecessary, says the Domestic Policy Council, which advises President Bush.

11 Jan

The US House of Representatives votes to ease restrictions on stem cell research, but falls 37 votes short of the majority needed to override President Bush's veto.



11 Jan

Britain's Human Fertilisation and Embryology Authority postpones a decision on whether scientists should be allowed to create so-called chimeras by mixing human genetic material with animal eggs, opting instead to consult the public.

9 Jan

Jong-Hyuk Park , former University of Pittsburgh researcher and Woo-Suk Hwang collaborator, falsified images in an unpublished report on monkey-derived embryonic stem cells, and will be barred for three years from applying for US government funds, the US Office of Research Integrity announces.

17 Jan

Cancer deaths fell slightly in 2004, suggesting that the 2003 drop—the first in 70 years—was more than a statistical fluke, the American Cancer Society announces.

18 Jan

Cigarette makers boosted nicotine levels by 11% between 1998 and 2005 in order to keep smokers addicted, Harvard University researchers report.

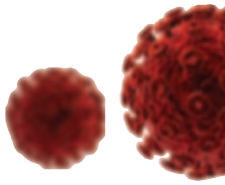
18 Jan

Responding to charges that entrenched departmental bureaucracies stifle collaboration and progress, Harvard University earmarks $50 million for interdisciplinary science research.

19 Jan

Mass immunization and surveillance caused worldwide measles deaths to fall by 60% between 1999 and 2005, exceeding the United Nations' goal of a 50% reduction, the World Health Organization reports (*Lancet* **369,** 191–200).

Gut warfare



Far from the unhurried killer it seemed to be, HIV is a swift assassin, gutting the body's immune system within days of infection. Erika Check finds out how this new paradigm is transforming AIDS research.

HIV is supposed to be a slow and stealthy killer. For years, scientists have thought the virus begins its assault in the blood, destroying just a few of its favorite targets—specialized immune cells called CD4 T-helper cells, which anchor the body's defenses against infections.

After that initial attack, HIV appears to move in slow motion, taking years to deplete enough CD4 cells to fatally decimate the immune system.

But in the 20 years that scientists have been studying AIDS, they haven't been able to explain this seemingly massive leap: how do so few infected cells drive the inexorable progression to death?

The answer may lie not in the blood, but in the gut.

Doctors have known for more than a decade that HIV affects the digestive system, causing intractable diarrhea and severe weight loss. But until recently, few had grasped the importance of those symptoms. Exactly how big a role the gut plays in the disease progression is still controversial, but a series of papers have redefined our understanding of how HIV kills and how to prevent it.

"We have ended up with a completely new view of HIV infection," says Daniel Douek, chief of human immunology at the US National Institute of Allergy and Infectious Diseases' Vaccine Research Center, who published some of those studies.

Far from being slow, all evidence now indicates that HIV's initial attack is swift and deadly, destroying CD4 cells in the gut where, in fact, most of the body's CD4 cells reside. In a monkey model, about 80% of CD4 cells in the gut are wiped out within the first four days of infection.

"There's been a complete turnaround," Douek says. "This has changed people's attitudes, from thinking that this disease is slow and indolent to thinking that it is extremely aggressive."

The fact that HIV's devastation happens so quickly suggests that the infection should be treated as early as possible and that vaccines should focus on generating immunity at mucosal surfaces, such as those that line the gut. It has also boosted interest in prevention strategies such as microbicides, which aim to block infections at the mucosal lining of the vagina.

"The work on the acute infection has led to a massive reappraisal of the mechanisms of disease pathogenesis, has helped refocus our views on where and when therapies should be instituted, and has led to the search for vaccines that elicit robust mucosal immunity," Douek says.

Digestive troubles

Why it took scientists so long to understand the gut's importance is a mystery in itself—particularly given that HIV researchers work more closely with clinicians than do researchers in most fields.

The reason may partly be that it is easier to study T cells in the blood than in the gut, and finding newly infected individuals is an impossible task. Still, there have been glaring signs from both monkey and human studies for more than a decade.

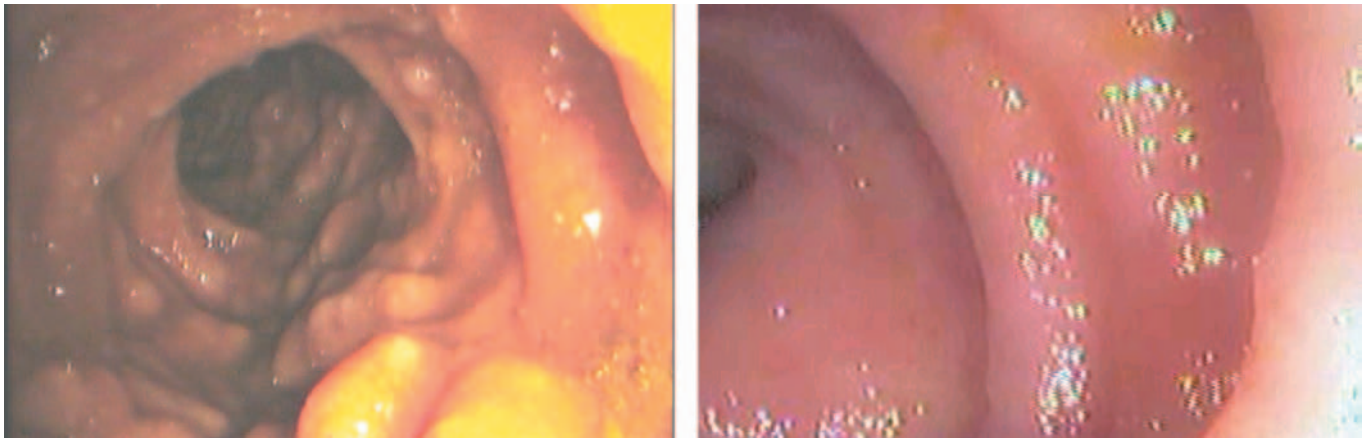
Digestive problems are a hallmark of AIDS—so much so that veterinarians always interpreted diarrhea in infected monkeys as a sign of full progression to the disease.

But in people, doctors assumed that gut problems were a result of opportunistic infections caused by the weakened immune system. "From the beginning, gut complications were very clearly linked to the disease, but most studies of gut tissue were focused on advanced infection," says Satya Dandekar, chair of medical microbiology and immunology at the University of California in Davis.

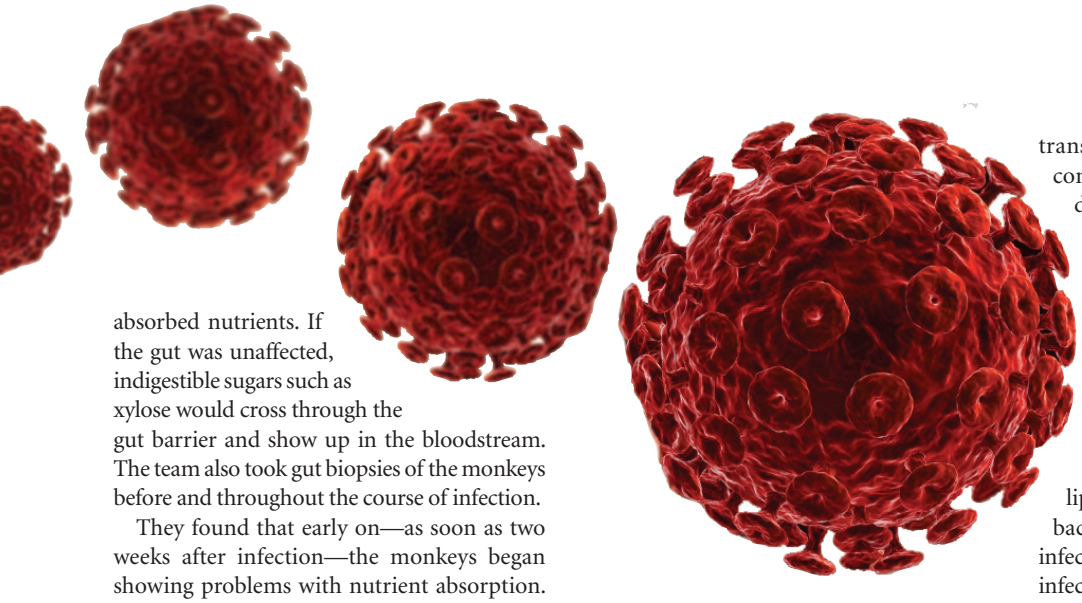
Most doctors never thought to order invasive tests, such as biopsies, to assess the virus's effect in the gut in early infection.

For people with HIV, the digestive problems were of serious concern. Dandekar noticed, for instance, that patients waiting to be seen by doctors would often have to run to the loo. To understand how HIV causes these gastrointestinal problems, Dandekar turned to rhesus macaques infected with the simian immunodeficiency virus, a relative of HIV that has been used to create monkey models of the disease.

As early as 1994, Dandekar's team began testing the gut lining by assessing how well it



Clean sweep: The gut harbors most of the body's CD4 immune cells (left), but HIV infection wipes them out (right).



absorbed nutrients. If the gut was unaffected, indigestible sugars such as xylose would cross through the gut barrier and show up in the bloodstream. The team also took gut biopsies of the monkeys before and throughout the course of infection.

They found that early on—as soon as two weeks after infection—the monkeys began showing problems with nutrient absorption. Gut biopsies revealed that large numbers of T cells and macrophages—which play a key role in fighting pathogens—are infected with SIV as soon as one week after infection (*J. Infect. Dis*. **169**, 1116–1120; 1994). These changes were apparent before complications such as diarrhea.

Four years later, Andrew Lackner and colleagues at the New England Regional Primate Center also showed that SIV has a quick, extensive and devastating impact in the monkey gut. In the rhesus macaque model, they found, SIV infection in the first two to three weeks of infection wipes out large numbers of CD4 T cells from the intestine—but not from the blood, spleen and other peripheral lymph organs (*Science* **280**, 427–431; 1998). The virus seemed to selectively destroy the protective mucosal lining of the gut.

"That really set the stage," says Douek. "But even that paper was overlooked."

Mucosal immunity

Over the following five years, Lackner and his colleagues showed that SIV preferentially targets T cells not only in the intestine, but also at other mucosal surfaces such as the lung and vagina, depleting the body's defenses at its primary barrier sites.

Finally, in 2004, Douek's group, in collaboration with researchers at New York's Aaron Diamond AIDS Research Center, published results that made it impossible to overlook the gut's importance.

Scanning intestinal biopsies of individuals recently infected with HIV, they found that all the observations in the SIV model hold true in people as well: the intestine is the first site of CD4 cell depletion, and memory T cells in the gut are wiped out early in infection (*J Exp. Med.* **200**, 761–770; 2004, *J. Exp. Med*. **200**, 749–759; 2004).

"[This] supports a simple hypothesis to explain much of the pathogenesis of HIV infection… that disease progression may correlate with turnover of specific cell subsets in mucosal tissues," Veazey and Lackner wrote in a commentary on the two papers (*J. Exp. Med.* **200**, 697–700; 2004).

It's still not entirely clear how the HIV's invasion of the gut leads to an overall immune failure.

In 2005, Dandekar's group reported a study on people who are infected for years with HIV, but who seem to keep the virus at bay—so-called long-term non-progressors. The group found that these non-progressors have normal levels of CD4 T cells in the blood and the gut. They also found that genes associated with inflammation and immune activation—the state in which the immune system is turned on to respond to an infection—are expressed at lower levels in non-progressors than in infected individuals who were losing the fight against the virus. This constant state of immune activation is thought to eventually exhaust the immune system of HIV-infected individuals.

But in both the non-progressors and susceptible individuals, genes associated with digestive functions are expressed at lower levels, indicating that the gut of non-progressors is also affected by the virus (*Proc. Natl. Acad. Sci.* **102** 9860–9865; 2005).

There is some evidence that this effect doesn't improve even with treatment. Even after years of retroviral therapy, as many as 70% of those infected still have depleted T-cell populations in the colon, even though T cells in the blood bounce back—suggesting that a blood T-cell count may not always accurately reflect the severity of the disease.

Despite all these pieces of information, however, it's not clear how the gut depletion affects the course of the disease.

Leaky gut

One theory, proposed in November 2006 by Douek, has to do with 'microbial translocation'—a concept well known in conditions such as inflammatory bowel disease, but foreign to most HIV researchers.

Microbial translocation is, as Douek puts it, "a leaky gut"—a condition in which the gut barrier ceases to function normally, and the enormous amount of bacteria normally found in the gut swarms out of the intestines and into the blood.

Douek measured levels of lipopolysaccharides, a component of the bacterial cell wall, in the blood of HIV-infected individuals. Those with chronic HIV infection—and monkeys infected with SIV—have elevated levels of blood lipopolysaccharides. Higher amounts of these substances correlate with higher levels of immune activation. The levels of lipopolysaccharides also drop after antiretroviral treatment (*Nat. Med.* **12**, 1365–1371; 2006).

"We think microbial translocation causes systemic immune activation and therefore progression in HIV disease," Douek says.

Douek's idea has its share of supporters and skeptics. But in the meantime, there is a stronger emphasis on mucosal immunity within the field. The National Institutes of Health and the Bill and Melinda Gates Foundation are both, for instance, funding attempts to make a vaccine that generates mucosal immunity and microbicides, which work at mucosal surfaces.

If Douek is right, antibacterial drugs could be given along with antiretroviral therapy to combat the leaky gut.

But it is too early to start advising doctors to change the way they treat people with HIV, says Marty Markowitz, researcher at the Aaron Diamond AIDS Research Center.

"At this point, there's no indication at all that treatment approaches should be changed," Markowitz says. "But I do think the field is remiss in not identifying enough patients in acute and early infection."

Still, the fact that researchers have finally begun paying attention to the gut might elicit some answers—and changes in the way HIV is treated. And that change is long overdue, says Dandekar.

When she first decided to look at HIV in the gut, senior faculty members advised her against it. "They said, 'Why are you working in the gastrointestinal tract?'" Dandekar recalls. "'Work on the lymph nodes instead.'"

Had she and others heeded that advice, Dandekar says, it may have taken even longer to realize the gut's importance. "I'm glad I didn't listen," she says. "I listened to my gut."

Erika Check writes for Nature Medicine from San Francisco.