

## COMING //

- **THROUGH SEPTEMBER 28:** "Gregor Mendel: Planting the Seeds of Genetics," an exhibit at the Academy of Natural Sciences in Philadelphia, will celebrate the nineteenth-century friar who introduced the world to heredity. On display: rare books from the abbey where Mendel studied as well as art inspired by genetics.
- **SEPTEMBER 30:** By this date, the FDA plans to fill 1,300 open positions. The hiring push is spurred in part by expansion of the agency's scope following the passage of the FDA Amendments Act of 2007. On the list of in-demand occupations: medical officers, nurse consultants and epidemiologists.



SUSANA SOARES

**FOCUS // BEES BECOME DIAGNOSTICIANS** in a glass instrument designed by artist Susana Soares. The insects, which have exquisitely sensitive antennae, can be trained to show a Pavlovian response to odorous molecules that indicate a single physiological factor, such as ovulation, or a disease state, such as tuberculosis (as in the instrument shown). When a user blows into the object, the bees either are attracted to the chamber holding the breath (signaling a positive result) or ignore it completely (negative). Future targets could include lung cancer and diabetes.

INTERVIEW //

**The Power of No**

■ BY ANITA SLOMSKI

*When chatting with colleagues at scientific meetings, postdoctoral student Christian Pfeffer often found that they had conducted the same experiments he had—with the same negative outcomes. Convinced of the need for a forum to discuss such failures, Pfeffer and his mentor, Bjorn R. Olsen, professor of cell biology at Harvard Medical School and dean for research at the Harvard School of Dental Medicine, found a willing publisher in London-based BioMed Central and, in September 2002, launched the online Journal of Negative Results in Biomedicine. The journal challenges scientists to rethink their experimental designs and questions, and encourages physicians to re-evaluate clinical practices based on negative data.*

**Q: What kind of negative results does your journal publish?**

**Olsen:** It covers the spectrum of negative results—though “negative” is a misnomer because in the long run the results may turn out to be positive. Some contradict what scientists believe are well-founded tenets and dogmas. Barbara McClintock, for example, spent decades showing that genes can pop in and out of the genome in different locations. That work, for which she eventually won the Nobel Prize, disproved the prevailing view that the genome is very stable. Others may rule out an



effect of a drug that was implied by the results of previous, imperfect studies, such as the idea that estrogen should be used to treat osteoporosis in women.

**Q: What about critics who say it's a waste of time reading about what isn't right?**

**Pfeffer:** Information, whether it

supports or contradicts an idea, is what drives science forward. The philosopher Karl Popper pointed out that only one black swan was needed to repudiate the theory that all swans are white, which is what Europeans believed for thousands of years until the exploration of Australia introduced them to black swans.

**Olsen:** Science is not about finding

truth in an absolute sense. It's about solving problems and developing the best possible explanations for specific questions. So it's important to consider a range of data, from the most "negative" to the most "positive." When Thor Heyerdahl sailed across the Pacific to Polynesia on the *Kon-*

## ■ Only one black swan was needed to repudiate the theory that all swans are white, which is what Europeans believed for thousands of years.

*Tiki* raft in 1947, he didn't prove that those islands were populated by people coming from South America instead of from Asia, as was commonly thought. But he did open the possibility, which forced experts to consider options other than the prevailing view.

**Q: You typically publish one to four articles a month, which isn't very many.**

**Olsen:** We don't get a huge number of submissions, which isn't surprising because most researchers tend to look for data that have a positive thread. Plus, postdocs and young faculty members who want tenure try very hard to publish in high-impact journals, and that isn't our journal yet. But five years from now, if the journal continues to attract scientifically defensible articles, then I would consider it to be successful.

**Q: Have changes in biomedical and life-science research made this journal more relevant today than it would have been 15 years ago?**

**Pfeffer:** Sophisticated screening techniques today, such as those that scan the entire genome, create a flood of data, all of which can be interpreted

in several ways. Asking which genes are altered by a cancer metastasis, for example, will produce a plethora of genes, but not all will follow the cellular processes we expect to see, and we may not yet understand how these cellular processes are linked. So researchers have become more open to publishing these controversial or ill-fitting results, which can contribute valuable information about a biological process.

**Olsen:** Also, some of the most exciting discoveries are occurring at the boundaries between classical scientific disciplines. For example, the fields of molecular biology and medicine are coming together to uncover the molecular basis of diseases. When scientists venture into areas where they are less experienced, they need to be open to both positive and negative results. ■

### BY THE NUMBERS //

## Bloodless Revolution

**\$350** Typical cost to transfuse one unit of blood

**0-2** Units of red blood cells typically used in open-heart surgery

**66** Estimated percentage of blood transfusions potentially administered unnecessarily, according to a study in the *New England Journal of Medicine*

**1878** Year when physician George Hayman perfected saline solution as a substitute for blood; generally considered the dawn of bloodless medicine, a movement that eschews donor (allogeneic) blood

**7:26** Verse in Leviticus stating, "Ye shall eat no manner of blood, whether it be of fowl or of beast, in any of your dwellings," which Jehovah's Witnesses believe prohibits them from accepting allogeneic blood

**2** Decades during which bloodless medicine has changed from being primarily patient driven (for religious or personal reasons) to being championed by doctors concerned about the rising costs and overuse of blood transfusions

**125** Approximate number of U.S. hospitals with bloodless surgery/blood management programs

**1974** Year marking the invention of the cell-salvage machine, which is used in bloodless surgery to clean and recycle blood

**23** Percentage increase in post-operative complications among heart surgery patients who received transfusions vs. those who did not ■

INFOGRAPHIC //

## Flu Central

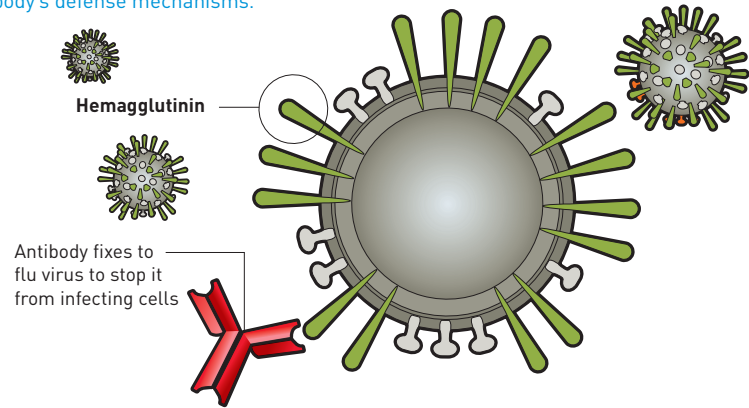
■ BY JENNIFER BAILS // INFOGRAPHIC BY FLYING CHILLI

Each February the World Health Organization announces the strains of influenza expected to circulate in the Northern Hemisphere the following winter—and thus identifies which should be targeted by the year’s flu vaccine. WHO’s projection requires calculated guesswork; the flu virus is constantly evolving, accumulating small mutations through a process called antigenic drift. What’s more, because it takes months to make, test and distribute the flu shot, the forecast must be made nearly a year in advance. The stakes of prediction are high; each year, seasonal flu sickens hundreds of millions of people and kills some 500,000.

A recent study published in *Science* sheds new light on how flu viruses evolve and migrate around the world. Armed with this knowledge, scientists may be able to refine their forecasts of the flu strains most likely to cause epidemics and to better select viruses for the vaccine.

### Have Drift, Will Travel

For the *Science* study, an international team led by Colin Russell and Derek Smith, both of the University of Cambridge, analyzed 13,000 samples of influenza A (H3N2) virus—the major cause of flu-related illness and death—that WHO’s Global Influenza Surveillance Network had collected across six continents from 2002 to 2007. Specifically, the team measured how well each sample bound to antibodies against a protein called hemagglutinin, which is found on the virus coat. Hemagglutinin triggers the body’s immune response to flu; changes in this antigen can allow the virus to escape the body’s defense mechanisms.

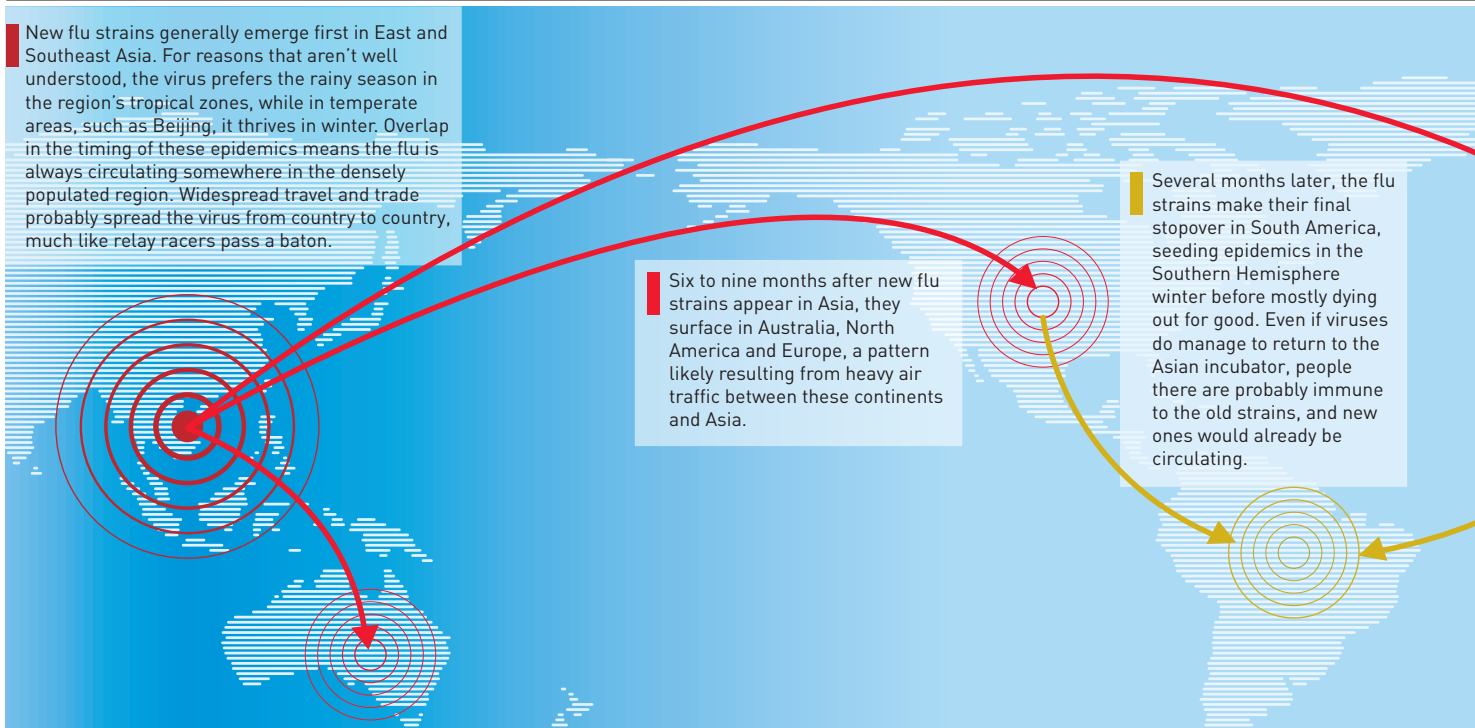


### From Asian Cradle to South American Grave

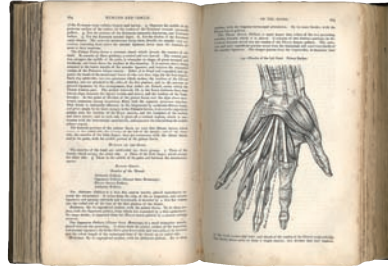
New flu strains generally emerge first in East and Southeast Asia. For reasons that aren’t well understood, the virus prefers the rainy season in the region’s tropical zones, while in temperate areas, such as Beijing, it thrives in winter. Overlap in the timing of these epidemics means the flu is always circulating somewhere in the densely populated region. Widespread travel and trade probably spread the virus from country to country, much like relay racers pass a baton.

Six to nine months after new flu strains appear in Asia, they surface in Australia, North America and Europe, a pattern likely resulting from heavy air traffic between these continents and Asia.

Several months later, the flu strains make their final stopover in South America, seeding epidemics in the Southern Hemisphere winter before mostly dying out for good. Even if viruses do manage to return to the Asian incubator, people there are probably immune to the old strains, and new ones would already be circulating.



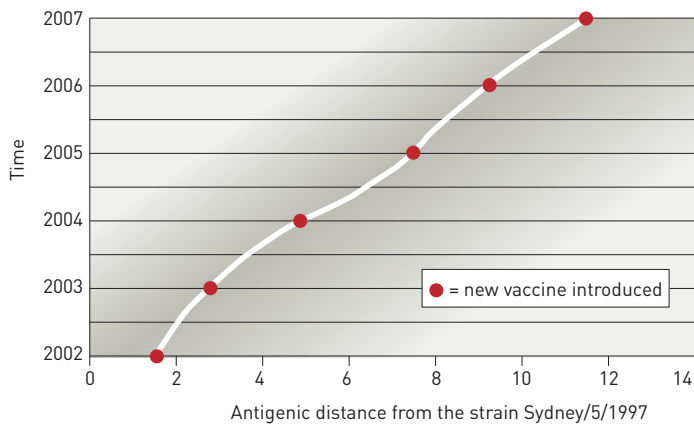
## Anatomy of Gray's



originally received equal billing, a later editor removed his name in 1909 for reasons unknown.)

Gray's was not the first text of its kind, but it gained acclaim for the clarity of its descriptions and

The scientists plotted their binding data on a new type of map that plots "antigenic distances," tracing alterations to the hemagglutinin in their samples during the five-year study. They found that the samples changed by at least two units of antigenic distance per year, thus warranting modifications to the vaccine. These analyses also allowed the researchers to track the spread of flu strains around the globe.



### Refining Prediction

When the viruses in the influenza vaccine are well matched to the predominant circulating strains, the flu shot is 70% to 90% effective, as has been the case in 16 of the last 20 U.S. influenza seasons. But last year, two of the three strains were not good matches, and the vaccine was only 44% effective.

Because the shape of the hemagglutinin molecule largely determines the corresponding antibody, it is the only portion of the virus WHO routinely sequences. Expanded sequencing of whole genomes could provide additional markers for tracking the flu. Researchers in the United States and England are now doing exactly that—and, crucially, stepping up surveillance in Asia.

In Galen's Greece, dissecting a human corpse was strictly taboo. To gain insight into the human body, anatomists instead dissected monkeys, dogs and pigs, an approach that led to certain misconceptions. Galen, for example, thought the human liver had five lobes like a dog's, rather than two.

During the sixteenth century, the Belgian anatomist Andreas Vesalius corrected many of the ancients' errors. Having dissected unclaimed corpses and the bodies of executed criminals, he authored the first heavily illustrated anatomy book. Still, the study of anatomy held no practical value until the mid-nineteenth century, when chloroform, the earliest anesthetic, was discovered. The surgeon's territory widened to many new areas of the body; as a result, medical students had much more to learn.

Henry Gray, a surgeon and lecturer at St. George's Hospital in London, saw the need for a new sort of medical textbook. He invited Henry Vandyke Carter, a fellow anatomist and talented illustrator, to co-create what has become perhaps the most famous medical text. First published 150 years ago, *Anatomy Descriptive and Surgical Anatomy* and was officially so named in 1938. (Though Carter

the beauty of its illustrations. Carter and Gray had dissected countless cadavers, using little from previous textbooks. The book was larger than the typical pocket-size medical text, making the illustrations more readable. For further ease of use, Carter labeled anatomical structures with their names rather than with tiny numbers that obliged the reader to flip to a key elsewhere in the book, as was customary. And at 28 shillings it was eminently affordable.

Since 1858, it has been translated into more than a dozen languages and has sold millions of copies worldwide. Each new edition is a little bulkier than the last as medical knowledge continues to expand—and each bears less and less resemblance to the original. The current edition (the thirty-ninth) includes high-resolution CT scans of tiny anatomical elements such as the inner ear's petrous bone, which Gray and Carter could not have observed. It also comes with a CD-ROM that provides nine "fully rotatable, strippable anatomical models," as well as a regularly updated online component. Alas, all of Carter's wood-block illustrations have been replaced by scans, photos and other drawings, and very few words are Gray's. ■



POLICY WATCH //

## Eyeing Clinical Trials

■ BY DEBORAH KELLY

Anyone with a life-threatening disease hoping to keep up with research into her condition is at several disadvantages. To learn the outcome of a clinical trial, she can read about it only in a journal, and because there are too many research papers for too few journals, many studies go unpublished. What's more, if the study's results are negative, drugmakers who sponsored the trial might choose not to publish the results or might even suppress them, as was allegedly the case with Vioxx, a pain reliever that was voluntarily withdrawn from the market in 2004.

To remedy this lack of transparency, the United States will become the first nation to launch a database of results of clinical trials that involve drugs, medical devices and biologics (products derived from living sources, such as vaccines). The data will be available online within one year of a study's completion or within 30 days of Food and Drug Administration approval. When the database debuts on September 27, it will include trials that were under way as of

or after Sept. 27, 2007. (Researchers who conducted trials of drugs that have been on the market for years are encouraged, but not required, to post their results.) The law threatens significant penalties—including withholding of federal funding and up to \$10,000 per violation—for drugmakers and other researchers who fail to submit the required data.

Trial results, except for those involving Phase I investigations (which determine the basic safety and dosage range of a drug or product, and which were left out because of political compromise and practical considerations, such as protecting researchers' intellectual property rights), will be posted at [ClinicalTrials.gov](http://ClinicalTrials.gov). The site now records such details as study design and outcome measures of more than 56,000 trials but no results.

The database is good news in at least one respect, says Bob Helms, founder of Guinea Pig Zero, a job zine for trial participants. Under the new law, sponsors will find it harder to conceal unexpected or dangerous reactions to drugs that could put future volunteers at risk. But Helms warns of a possible unintended consequence: more exporting of the clinical trials industry. Trial sponsors "might take research units to places like India and Russia, where the rules are almost mythical, if they exist at all," he says. Deborah A. Zarin, director of [ClinicalTrials.gov](http://ClinicalTrials.gov), confirms that if a trial is conducted entirely outside the United States and the drug under study is not manufactured here, the FDA would have no regulatory authority.

Critics question how the lay public will be able to interpret results that haven't been peer reviewed and thoroughly discussed in medical journals. On the upside, Zarin notes, the structure of the results database—with fill-in fields and little room for commentary—will keep spin to a minimum.

Researchers' responsibilities will expand in September 2009, when they must begin reporting serious and frequent adverse events. And by the following year, the Department of Health and Human Services will have to develop regulations to further expand the database, including full protocols (such as a summary of the study's purpose) or additional information to better evaluate results.

Meanwhile, the movement toward greater research transparency is gaining converts around the globe, and the World Health Organization recently conducted a survey to help craft a global standard for publicizing trial results. Zarin says, "The rest of the world could benefit by observing the effects of this national experiment." ■

## ADVANCES // Hide and Seek

**TO STAVE OFF** bacterial infection, white blood cells engulf and destroy germs with powerful digestive enzymes—a process the wily tuberculosis bacterium often manages to evade. Now researchers at the University of British Columbia and Vancouver Coastal Health Research Institute have discovered how. *Mycobacterium tuberculosis* secretes a protein, PtpA, that acts directly on a white-blood-cell signaling protein to keep it from sending out its “digest and destroy” message, allowing the germ to invade and multiply in the white blood cell. Researchers have already engineered an antibody that blocks the protein, which they hope will become a basis for therapy.

[www.cellhostandmicrobe.com](http://www.cellhostandmicrobe.com); search for “tuberculosis” and “33b”

**FORGOING HEART SURGERY** to avoid the oft-reported side effect of memory lapse is an option many patients have considered. But Johns Hopkins researchers who compared the cognitive function of patients receiving surgery with that of patients who received nonsurgical treatments suggest that surgery was not to blame. During six years post-treatment, both groups experienced an almost identical decline in cognitive function.

[www3.interscience.wiley.com/journal/119140421/abstract](http://www3.interscience.wiley.com/journal/119140421/abstract)

**STEREOSCOPIC GLASSES**, inspired by the technology that video gamers use to simulate depth perception, could become a tool for operating on a beating heart. A surgeon at Children’s Hospital Boston repaired 32 atrial septal defects in pigs using standard 3-D ultrasound guidance alone, then donned the glasses for another 32 procedures. With the depth perception the glasses provide, he was 44% faster, as reported in *The Journal of Thoracic and Cardiovascular Surgery*.

[jtc.ctsnetjournals.org/cgi/content/full/135/6/1334](http://jtc.ctsnetjournals.org/cgi/content/full/135/6/1334)



### DEFINED //

**plug and play** [ˈplæg ən(d) ˈplā] n: a term that originally referred to the configuration of various consumer electronics to communicate with each other without the user’s involvement, and that is now gaining currency within health care, referring to the interoperability of medical devices to improve safety and efficiency.

If a patient on a ventilator requires a chest X-ray, an operator may need to shut off the ventilator briefly to prevent her lung movement from blurring the image, and there’s a risk the operator will forget to restart the ventilator. But what if the two machines could synchronize efforts, ruling out the chance of human error? Such are the scenarios under study by the Medical Device “Plug-and-Play” Interoperability Program started in 2004. A collaboration between the Massachusetts General Hospital, the Partners HealthCare Information System, the Department of Defense and Boston health care technology consortium CIMIT, the initiative has brought together doctors, engineers, other health care delivery systems, medical device manufacturers and government agencies, such as the FDA, which regulates medical instruments.

Julian M. Goldman, an anesthesiologist at the MGH and the program’s director, estimates that the first plug-and-play products will appear within three years. He expects that plug-and-play devices will eventually operate throughout hospitals, most notably in areas providing acute care, where they could significantly improve patient safety. ■

**A MYSTERIOUS MOLECULE** in the liver, called the Ashwell receptor, seems to play a crucial role in fighting infection. Researchers at the University of California, San Diego School of Medicine discovered that the receptor reduces levels of blood-coagulating factors to help the body combat the lethal blood clotting caused by sepsis. In theory, then, a drug designed to boost supply of the molecule might decrease mortality from sepsis and other blood infections.

[nature.com/nm/journal/v14/n6/full/nm0608-606.html](http://nature.com/nm/journal/v14/n6/full/nm0608-606.html)

**PERIODONTAL DISEASE**, already linked to heart disease and diabetes, has now been implicated in cancer. In a study by researchers at Imperial College London, subjects with a history of the gum disease had a 14% higher incidence of cancer than those without. Begun in 1986, the research included more than 48,000 males who answered questionnaires about oral hygiene every two years. Follow-up studies are needed to confirm the results and to determine whether the same holds for female subjects. But the researchers say that reducing any risk conferred by this link is as easy as flossing.

[thelancet.com](http://thelancet.com); search for “Imperial College,” “periodontal” and “cancer”

**A TENACIOUS STOMACH BACTERIUM** may find a beneficial use—as a carrier for the flu vaccine. Barry J. Marshall, who won a Nobel Prize for his discovery of *Helicobacter pylori*, infected mice with a flu-carrying form of *H. pylori*. The bacterium colonized the animals’ stomachs and generated antibodies to fight the flu, as reported in the journal *Helicobacter*. This year, in the first round of trials, Marshall plans to remove and then replace the germ in healthy subjects’ stomachs to see how their immune systems respond; if successful, he’ll test the flu-carrying form. Eventually he hopes to develop a commercial yogurtlike drink to easily administer the vaccine.

[blackwell-synergy.com](http://blackwell-synergy.com); search for “helicobacter” and “vaccine” ■