



Current Topics

Zoological Database Serves as Warning System for Infectious Diseases

Zoos and aquariums typically monitor animals under their care for infectious diseases, and often share information about outbreaks with the International Species Inventory System (ISIS) in Eagan, Minn. With the aim of developing a global warning system for zoonotic infectious disease outbreaks, ISIS launched an effort several years ago to develop a zoological information management system (ZIMS) (<http://www.isis.org/Cms/Home/content/zims>). Once ready later this year, it will be accessible anywhere in the world to any ISIS member institutions having computers with Internet access. Currently, ZIMS is undergoing extensive testing and, once in place, it will be used for detecting infectious diseases among animals, including rabies, SARS, avian flu, or chronic wasting disease, that are potentially communicable to humans.

ISIS collects information from 767 zoos and aquariums in 72 different countries. For the past two decades, that information was archived in two databases, the Animal Records Keeping System (ARKS) for tracking individual animals and the other, Medical Animal Record Keeping System (MedARKS), for keeping clinical records, including pathologies, parasitology treatments, and vaccinations. Since the Bronx Zoo first found West Nile virus in North America in 1999, zoos around the world have become more actively involved with disease surveillance and diagnosis. However, because neither ARKS nor MedARKS can be used to communicate with other ISIS

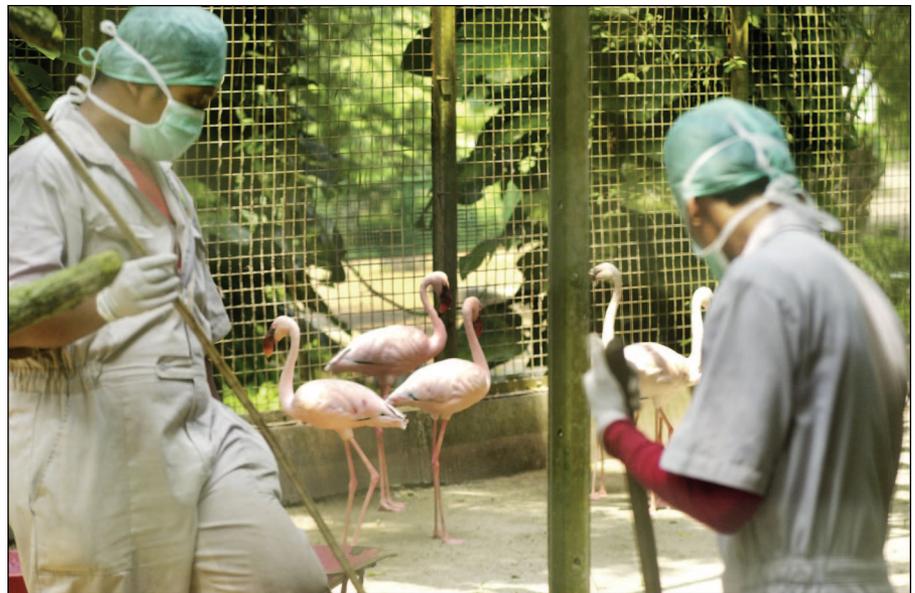
institutions, veterinarians were stuck with more cumbersome e-mails or phone calls when they wanted to notify colleagues of disease outbreaks.

One of the daunting tasks in developing the ZIMS system involved converting data from several predecessor systems that had been collected during the past two decades into a format that is suited for the new database. The older systems included 9 million animal records, 1 million prescriptions, and 0.5 million serum and blood records, according to Paul Calle, a veterinarian at the Bronx Zoo and Wildlife Conservation Society, both in Bronx, N.Y., who is helping to develop some of the clinical screens that will be used in the new system.

“ZIMS will provide for the first time, the rapid sharing and examination of medical and animal record in-

formation on a global basis,” Calle says. Here is how the system is expected to work: if unusually high numbers of bird deaths occur in a particular city, local health officials could request nearby ISIS member institutions to review ZIMS to determine whether those deaths are part of an isolated incident or a larger-scale outbreak of avian flu, West Nile, or some other virus. Another scenario might be a zoo reporting the finding of anthrax. Participating ISIS members could then coordinate their efforts to help determine whether it represents a naturally occurring background level or a spike that should be reported to federal officials.

Like zoos, aquariums continuously monitor their collections to protect their animals from disease. Should a disease outbreak be encountered, a



Zoonotic infectious diseases can show up in zoo animals such as these flamingos at the Ragunan Zoo in Jakarta, Indonesia, in September 2005, when 19 zoo birds died of avian influenza. A new system, the Zoological Information Management System, is being developed to help track such diseases. (AP Photo/Irwin Fedriansyah.)

qualified veterinarian enters data into a ZIMS disease alert field and sends an e-mail message to all participating ISIS members.

When ZIMS is released, it will be available in three slightly different versions to suit the varied needs of participants. One version works like a bank or airline reservation system, allowing users to access the Web and carry out transactions, while another more advanced version is designed for use in a large institution with many users. The third version is for use on a single computer for institutions with limited resources and internet connectivity. A workshop planned for mid-year will develop a plan that “allows ISIS to serve the needs of public health while preserving our members’ total confidence in the privacy of their data,” says Jaime Meyer of ISIS.

Barry E. DiGregorio

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Does Viral Fusion Cause Aneuploidy and Cancer?

Although largely overlooked as a cause of cancer, viruses that induce cell fusion may contribute more to this disease than is commonly thought, according to Yuri Lazebnik and his colleagues at Cold Spring Harbor Laboratory in Cold Spring Harbor, N.Y. Their recent findings suggest that viral fusion should be considered along with other virus-associated activities that disrupt host cells, including viruses that insert oncogenes or integrate their own genes into host genomes, as a potential basis for cancer.

Mammalian cells that are multinucleated operate under constraints. For example, multinucleate muscle cells, once formed, do not proliferate. Moreover, when one virus-infected mammalian cell fuses with another, the resultant hybrid cells typically are even more constrained—in fact, they do not live long.

For example, when cultured human fibroblasts are infected with Mason-Pfizer monkey virus (MPMV), the cells that fuse soon die, according to Lazebnik. However, if such a fused cell also contains a cell cycle-disrupting oncogene, such as E1A or human ras-1, then large numbers of the fused cells proliferate, developing chromosomal aberrations along with behaviors like those observed in cancer cells. Moreover, when these aneuploid cells are transplanted into mice, the animals develop carcinoma-like tumors. Details of these experiments appear in the March 6, 2007, issue of *Current Biology*.

Indeed, E1A and ras-1 are oncogenes, “but even if expressed together they are insufficient to make cells tumorigenic,” notes Lazebnik. The combination of an oncogene and a fusogenic virus appears necessary to produce cancers. Some type of synergy occurs between viral fusion and oncogenes to induce chromosomal instability.

Aneuploid cells, in which chromosomes are abnormal in number or structure, are commonly found in solid tumors. One tentative explanation is that cell cycle-disrupting mutations generate aneuploid cells. Although less widely recognized, cell fusions also can give rise to aneuploidy by destabilizing the host cell chromosomes by means of deletions, insertions, inversions, or translocations. “More than a hundred years ago, scientists had the idea that chromosome instability causes cancer,” says Lazebnik. One source of that instability could be virus-induced cell fusions.

At least 18 of 29 virus families that infect human cells have fusogenic members, including herpes, influenza, Epstein-Barr, rubeola, and respiratory syncytial viruses, and thus could generate chromosomal instabilities that lead to cancer. If these or other fusogenic viruses contribute to cancer, immunizing against them may also pro-

tect against cancer, much as the recently developed vaccine for human papillomavirus (HPV) prevents cervical cancer and the hepatitis B vaccine prevents liver cancer.

Similarly, any use of fusogenic viruses as vectors to deliver gene therapy should raise safety questions. However, Lazebnik says, “No one considers whether retroviral vectors could cause fusion, because fusion is not considered a pathogenic process.”

“It’s a fascinating possibility that cell fusion could lead to tumorigenesis,” says oncologist David Pellman at the Dana-Farber Cancer Institute and Harvard Medical School in Boston, Mass. As an oncologist, he suspects that many cancers have a viral cause. However, viruses are rarely detected in cancers, probably because they hit and run—perhaps acting according to the mechanism that Lazebnik proposes, which could explain why viruses are never found. But it’s an unproven idea at this point. Although “a transient virus may cause fusion,” for example, in the case of childhood leukemia, Pellman adds, “there’s no direct evidence whether viral fusion is epidemiologically meaningful.”

Carol Potera

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Expanding Biodefense Research Leading to Opportunities Plus Unease

It is unsettling to view slides explicitly labeled “unclassified” during a matter-of-fact talk on food safety issues, even in the context of a biodefense meeting—in this case, during the 4th ASM Biodefense & Emerging Diseases Research Meeting, held in Washington, D.C., last March. Although most attendees seemed not to notice, a few critics of the recent biodefense research buildup voiced concerns that some of these federal programs lack transparency and are



National Academy Report Urges Major Microbial Metagenomics Initiative

Metagenomics presents the greatest opportunity since the invention of the microscope to revolutionize our understanding of the microbial world, according to a report from the National Research Council of the National Academies (NA) in Washington, D.C. The report, "The New Science of Metagenomics: Revealing the Secrets of Our Microbial Planet," recommends a global initiative, including several large-scale, internationally coordinated projects and numerous medium- and small-size studies, to drive advances in this field. The recommended large projects could be organized through "virtual" centers involving scientists at many locations around the world, and would probably need to be sustained for 10 years, the report notes. These projects would serve as incubators for developing novel techniques and databases to be used also by investigators running smaller experiments. In addition, the large studies would provide the "big science" appeal that is often useful in igniting public interest. Jo Handelsman of the University of Wisconsin, Madison, and James M. Tiedje of Michigan State University, East Lansing, cochaired the committee that wrote the report, which was released last March and may be ordered via the NA website (<http://www.nap.edu>).

sending the wrong signals about U.S. intentions.

There is also a concern that scientists working in this sector are not seeing the bigger picture. "[That] the crowd at the ASM [biodefense] meeting [is] not commenting on anything is disappointing," says Laura Kahn of the Program on Science and Global Security at Princeton University in Princeton, N.J. "I've gone to all four of these ASM meetings and, this year, the participants were particularly nonvocal."

Of course, taciturn microbiologists may find themselves well suited to working in biodefense areas where there are employment opportunities these days—namely, with the intelligence community. Its members are faced with "leveraging [their] expertise to better understand the biothreat," says Lawrence Kerr who works in the Office of the Director of National Intelligence (DNI) in Washington, D.C. Although DNI taps out-

side experts to help it make "technical assessments," there is a "desperate need for scientists to come into this field."

The Department of Homeland Security (DHS) is another expanding outlet for microbiologists interested in evaluating biodefense-related issues. "We don't do a lot of countermeasures research, except to think how someone might try to avoid them," says Bernard Courtney of the DHS National Biodefense Analysis and Countermeasures Center (NBACC) in Frederick, Md. NBACC's review of 28 threat agents, completed early this year, focused on direct health consequences from the misuse of such agents, according to Courtney. A follow-up assessment will include a review of economic and social consequences from bioterror attacks involving such threat agents.

The current budget for DHS includes a request for \$228.9 million to protect against chemical and biological attacks, with emphasis on those

threat agents with the "greatest potential for widespread catastrophic damage," such as aerosolized anthrax and smallpox, according to recent congressional testimony from DHS Under Secretary for Science and Technology Jay Cohen.

Meanwhile, NBACC is building a 160,000-square-foot lab facility that is expected to be ready by mid-2008. Although it will include high-level containment space, the lab "will not be operated as a secret facility," Courtney says. However, some DHS research done there may be classified, according to him and other officials from the department. Reviews of those DHS research projects will be conducted by an internal "compliance review group," he says.

"I have a major concern with that compliance review group," says Kahn from Princeton. If DHS conducts internal reviews, it becomes difficult to show that the programs are in compliance with the international Biological Weapons Convention. More generally, she says, keeping these and other components of the federal biodefense research effort away from public view makes them increasingly difficult to distinguish from what would be needed for a bioweapons development program. For example, besides the possibility of DHS conducting classified research at its facilities in Frederick, Md., the department also has contracts for doing studies at nuclear weapons laboratories. "What signals does this send to the international community?" she asks. "With so little oversight and transparency, we may be moving down a path that we'll regret."

Jeffrey L. Fox

Jeffrey L. Fox is the *Microbe Current* Topics and Features Editor.

Can Insights into Specific Pathogens Lead to General Countermeasures?

Recent efforts to probe pathogens that are potential biowarfare agents and

their toxins are providing highly specific insights, and participants at the 4th ASM Biodefense & Emerging Diseases Research Meeting, held in Washington, D.C., last March, offered several fascinating recent examples. Yet one message from the keynote session, calling for broad countermeasures against such pathogens, almost seemed to challenge the value in the current search for such narrowly focused insights.

“The number of threat agents exceeds the number of products that can be developed,” says Thomas Monath, a consultant from Harvard, Mass., who is with the venture capital investment firm, Kleiner Perkins Caufield & Byers (KPCB) of Menlo Park, Calif. Hence, he recommends that researchers seek “broad-spectrum countermeasures” and “multivalent vaccines.” For instance, although there are 23 families of viruses that infect humans, “only 7 are responsible for most of the mischief, and they use only 5–8 different pathways into cells,” he says.

Early in 2006, KPBC established a \$200-million fund for investing in companies developing products to counteract, prevent, or, in some cases, detect or diagnose emerging infectious diseases.

A big challenge, of course, is going from information about particular pathogens to develop products with broad-spectrum activity. Any takers? Here are some insights into a handful of specific cases from the ASM conference last March. They are representative, by no means exclusive, and the list seems to be growing, not shrinking.

Consider the Chikungunya virus, whose changing patterns of infection and virulence are posing an increasing threat to human populations along the eastern coast of Africa, in India, and among islanders outward across the Indian and Pacific Oceans, according to Ann Powers of the Arbovirus Diseases Branch of the Centers for Disease Control and Prevention (CDC) in Fort Collins, Colo. About 2 million

individuals were infected with this virus during the past 2 years—generally subject to fevers, headaches, severe joint pain, but few deaths, she says.

Between 2005 and 2006, there was an extensive Chikungunya viral outbreak in La Reunion, Mauritius, in the southwestern Indian Ocean, affecting more than 255,000 individuals. More importantly, these surging infections were accompanied by a changing pattern of type and severity of attack, suggesting that a new genotype of virus might be emerging or a different insect is carrying the virus, she points out. Unusual features of this outbreak included neurologic symptoms, some deaths, and infections being transmitted to fetuses and newborns. “A very small number of changes in the virus may be all that’s responsible for these changes in patterns of disease,” she says.

Vibrio cholerae is a severe diarrhea-causing, waterborne bacterial pathogen in parts of that same region. Although its attack rate and other patterns have proved steady for several decades, researchers are learning that it carries a range of accessory toxins that make it a more persistent and thus more effective pathogen, according to Karla Satchell of Northwestern University Medical School in Chicago, Ill. In particular, the recently identified RTX toxin acts autocatalytically before somehow acting upon actin molecules that are a key part of the cytoskeleton in host cells, leading them to form crosslinks and those cells to become round. RTX and other “auxiliary” toxins may explain how some *V. cholerae* strains manage to be pathogenic even when lacking cholera toxin, she says.

Some of the mysteries underlying the specific toxic activity and particularly how botulinum toxin gravitates to target nerve cells are yielding to recent research efforts, according to Mauricio Montal of the University of California, San Diego. After it moves across the neuromuscular junction, it

Microbes Implicated in Human Behavioral Changes

In several separate developments, researchers linked human behaviors with the behavior of microorganisms in unexpected ways, including:

- Christopher Lowry of Bristol University in Bristol, United Kingdom, and his collaborators are testing whether challenging individuals with inactivated *Mycobacterium vaccae* can alleviate symptoms of depression. When such killed bacteria are injected into mice, they not only trigger an immune response but also induce the brain to produce serotonin, a neurotransmitter that is the target of the class of antidepressant drugs called serotonin-reuptake inhibitors. Details appear in 28 March 2007 online version of *Neuroscience* doi:10.1016/j.neuroscience.2007.01.067.
- Clinical researchers at the National Institute of Mental Health in Bethesda, Md., are enrolling patients in two studies of a set of pediatric autoimmune neuropsychiatric disorders that are associated with streptococcal infections. In one case, the researchers will be examining a potential link between the bacteria that cause strep throat and the onset of obsessive-compulsive disorder in some children. They suspect that antibodies mistakenly attack the basal ganglia, a set of structures at the base of the brain.



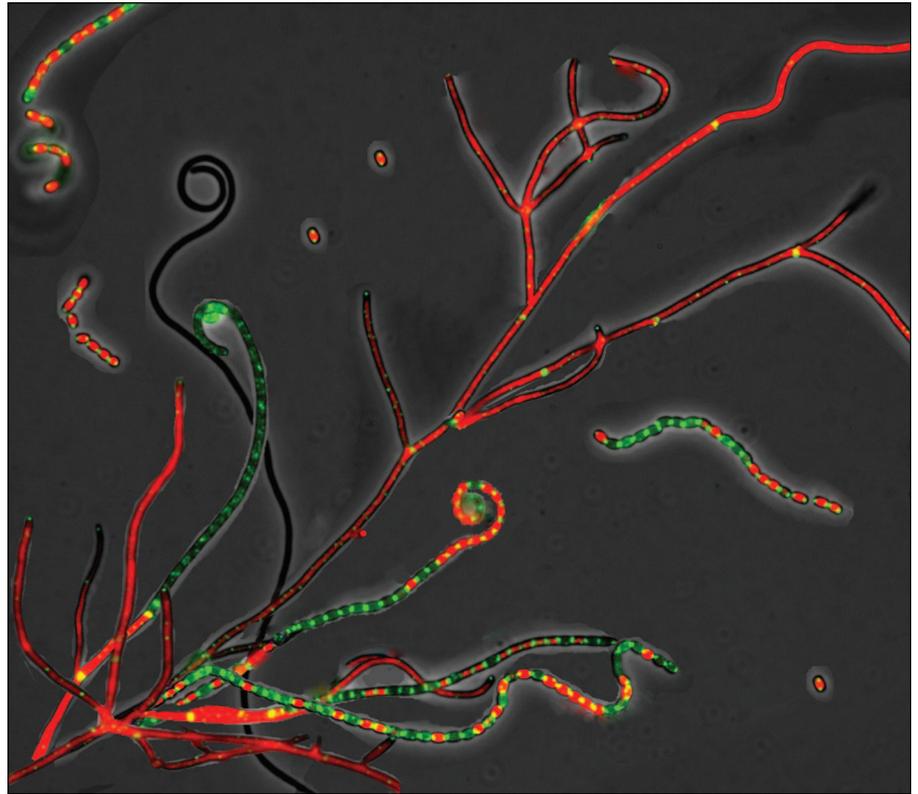
enters cells via endosomes, undergoes a conformational change, and eventually acts as a protease on host proteins that are situated in the cytoplasm. These actions depend, in part, on a portion of the toxin molecule acting as a channel that enables it to cross from one host cell compartment into another, he says. This translocation occurs “only under defined conditions and, once the translocation is completed, the channel is shut off,” he adds. “In principle, molecules that target this channel could help to control damages caused by botulinum toxin.”

Jeffrey L. Fox

Mechanism Explaining Low-Level Strep Resistance Raises Bigger Questions

Although high-level resistance to streptomycin arises from mutations in a ribosomal protein, the source of low-level resistance to this antibiotic remained obscure for several decades. Now that mystery is solved, although it raises several others, according to Kenji Nishimura, Susumu Okamoto, and others who work with Kozo Ochi at the National Food Research Institute, Tsukuba, Japan. They report that low-level streptomycin resistance arises because of a mutation to a gene encoding a specific methyl transferase that, in turn, leaves a particular nucleotide unmethylated at the site along the ribosome called the 530 loop. In this unmethylated state, the ribosome remains capable of making proteins even in the presence of streptomycin, which ordinarily blocks protein synthesis.

The mutation itself is in a gene encoding an enzyme that ordinarily modifies particular nucleotides. Specifically, Ochi says, “mutations in *rsmG* (rRNA small subunit methyltransferase gene G) result in low-level streptomycin resistance in *Streptomyces coelicolor*.” Besides making these bacteria resistant to streptomycin,



Streptomyces coelicolor hyphae. *S. coelicolor*'s mechanism of low-level resistance to streptomycin also boosts its production of another antibiotic, actinorhodin. (Image courtesy of Nora Ausmees, Uppsala University, Uppsala, Sweden.)

rsmG mutations boost production of another antibiotic, namely actinorhodin, by *S. coelicolor*. Further details appear in the May issue of the *Journal of Bacteriology* (189:3876–3883).

Since its discovery in 1944, streptomycin has been used widely for treating tuberculosis. According to Okamoto in Ochi's group, the biochemical mechanism that triggers low-level resistance to streptomycin in *S. coelicolor* also comes in play in other bacterial species, including *Mycobacterium tuberculosis*, whose version of the RsmG protein is functionally equivalent to the methyltransferase enzyme made by *S. coelicolor*. These similarities in the RsmG proteins may prove “useful to construct a strategy to develop novel drugs against tuberculosis,” Ochi notes.

Besides making several kinds of bacteria resistant to streptomycin, mutations in *rsmG* boost production of the unrelated antibiotic actino-

rhodin in *S. coelicolor*. This change “is intriguing in considering strategies for strain improvement,” and could well prove industrially useful as a means for improving the productivity of other antibiotic-producing bacterial strains, Ochi says.

It remains mysterious how introducing low-level resistance to streptomycin renders *S. coelicolor* more efficient in producing the unrelated antibiotic actinorhodin, according to Justin R. Nodwell of McMaster University in Hamilton, Ontario, Canada, whose commentary also appears in the May *Journal of Bacteriology*. Further, mutations in *rsmG* apparently overcome mutations in other genes that tend to dampen actinorhodin production. “What on earth is that all about?” he asks. Ochi interprets those changes as possibly “indicating ribosomal governance of gene expression” — which, if so, undercuts current dogma that DNA and messenger RNA

molecules (mRNA) direct ribosomes, not vice versa.

These results could be pieces of a still larger puzzle. "In addition to this apparent disconnect between biosynthesis and resistance, antibiotic production appears to be controlled by a regulatory network of truly Byzantine proportions," Nodwell notes. "To date, at least 18 genes have been shown to influence antibiotic production in *S. coelicolor*—a subset of these also control sporulation."

Other questions about the molecular behavior of these mutants remain unanswered. For example, the 530 loop of the bacterial ribosome ordinarily plays an important role during translation, helping to assure the accuracy of this process whereby proteins are made based on the accurate reading of mRNA. However, even though the 530 loop in the bacterial ribosome of the *rsmG* mutants remains unmethylated, there apparently is "no fitness cost," Ochi says. If correct, what is the biological effect of this methylation? Further, he notes, *S. coelicolor* "encodes proteins similar in sequence and mechanism to those that confer clinical resistance to vancomycin." Yet, vancomycin targets bacterial cell wall synthesis, not protein synthesis along ribosomes.

David Holzman

David Holzman is the *Microbe Journal* Highlights Editor.

Experts Urge FDA To Use Databases, Post-Market Monitoring To Boost Safety

"Approval is but one magic moment," says Chris Schroeder of Duke University School of Law in Durham, N.C., referring to the life cycle of drugs and other products that come before the Food and Drug Administration (FDA) for review before being licensed. During the past few years, however, safety concerns over several specific classes

Food for Thought on Foodborne Illnesses

Statistics reinforce a recent spate of news reports indicating that foodborne infections are steady or on the rise, according to a report released in April by officials at the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. For instance, the incidence of infections caused by *Escherichia coli* O157 and *Salmonella* was similar to 1996–1998, which was a period of high activity, according to CDC officials, citing FoodNet data from last year. One reason those infections are not falling may be that these pathogens are contaminating foods that previously were not associated with these diseases, such as spinach and peanut butter. Meanwhile, although *Campylobacter*, *Listeria*, *Shigella*, and *Yersinia* foodborne infections show a sustained decline in incidence compared to baseline data from 1996–1998, most of that decrease occurred between 1999 and 2002. Further details from the report, "Preliminary FoodNet Data on the Incidence of Infection with Pathogens Transmitted Commonly Through Food - 10 States, United States, 2006," are available online at www.cdc.gov/mmwr.

of drugs, including painkillers and antidepressants, led to approvals being revoked or to new warnings on product labels. Many experts are seeking alternative measures to ensure safety without unduly impeding the development of new products. If FDA had "stronger postapproval authority," he says, "it could take pressure off those approval decisions."

Schroeder joined several dozen experts who met last March during a "Symposium on the Future of Drug Safety," convened by the Institute of Medicine (IOM) in Washington, D.C. The symposium focused on a recent IOM report, "The Future of Drug Safety: Promoting and Protecting the Health of the Public," whose summary and recommendations are available online at <http://www.nap.edu/catalog/11750.html>. Many consider this an opportune time for instituting reforms at FDA because Congress is soon due to reevaluate the Prescription Drug Fee User Act, which provides resources and could expand authority for conducting product safety reviews.

One key recommendation in the IOM report is for FDA officials to

reevaluate products systematically within five years of receiving agency approval. Calling this reform "overdue," Robert Temple, director of the FDA Office of Drug Evaluation, says that waiting "five years is too late. We now have a pilot project to see if we can do that [reevaluation] much sooner."

Another recommendation calls on FDA to include staff from its Office of Surveillance Epidemiology (OSE) in every review of drug candidates. Although the agency is reviewing the feasibility of doing so, it would be "labor and resource intensive," says Ellis Unger, who is OSE deputy director for science. Another problem is that there is "not a great deal of clinical expertise among OSE staff."

Because he considers the traditional approach to developing drugs "broken," Garret Fitzgerald of the University of Pennsylvania School of Medicine in Philadelphia recommends training a new cadre of scientists who will develop an "integrated approach to personalized medicine," relying heavily on biomarkers to guide the development and regulation of new therapeutic products. Such efforts



Progress for Separate Products that Block Hepatitis B, C Viruses

Officials of the Food and Drug Administration in April approved an immune globulin, called HepaGam B, for preventing hepatitis B virus from reinfecting patients who receive liver transplants. In a clinical trial, HepaGam B, which is manufactured by Cangene Corp. of Winnipeg, Canada, reduced the virus recurrence rate from 86 to about 13% among patients who received liver transplants. In a separate development, the hepatitis C protease inhibitor, called telaprevir, when administered with pegylated interferon and ribavirin, gave high rates of response and enabled some patients infected with hepatitis C virus to clear that virus, according to John McHutchison, who directs gastroenterology and hepatology research at Duke Clinical Research Institute in Durham, N.C., and his collaborators. He reported interim results from clinical trials during the 42nd Annual Meeting of the European Association for the Study of the Liver, held in Barcelona, Spain, in April. Telaprevir is being developed by Vertex Pharmaceuticals of Cambridge, Mass., in collaboration with Tibotec Pharmaceuticals, Ltd., of Cork, Ireland.

would entail investing \$20 million per year for FDA and the National Institutes of Health (NIH) to train such specialists, he estimates.

Yet another recommendation is for FDA to make better and more systematic use of databases that compile information about adverse reactions or other clinical outcomes of patients taking various drugs. "I think this is feasible right now," says Mark Mc-

Clellan, who is a fellow at the AEI Brookings Joint Center for Regulatory Studies in Washington, D.C. He also is a former FDA Commissioner and former head of the federal Centers for Medicare and Medicaid Services.

Currently, the main post-marketing product surveillance system is "passive," McClellan says. Moreover, the agency also relies too heavily and too narrowly on information coming

from specific drug product databases that individual manufacturers maintain. Among other shortcomings, this approach "misses drug-class effects," he says. It also misses potentially valuable information that could be compiled from massive databases recording clinical experiences such as those maintained in both the private and public sectors, including by the Veterans Administration and the Department of Defense. He envisions "public-private collaborations to do the analyses, with independent research groups assisting FDA."

Others agree regarding the value in adapting large databases for the purpose of monitoring the safety of drugs and other FDA-regulated products. "We need populations of about 100 million to get answers quickly," says Richard Platt of Harvard Medical School in Boston, Mass. And, adds Robert Califf of the Duke University Medical Center, "A federated public-private model . . . is the only way to go [because] we need to evaluate large numbers of subjects for long periods." In terms of drug and device safety, he adds, "We are spending a lot of money in stupid ways. It's time to do something else and, if it's done right, industry costs will come down."

Jeffrey L. Fox