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Tuberculosis: Still a Global Challenge

I enjoyed in January’s issue of *Microbe* Bernard Dixon’s very graphic description of having had probable tuberculosis as a child. In particular, he wonderfully highlighted the horror of haemoptysis and both the bewilderment and suspicion of those looking after him. It reminded me very much of memories of my own father managing cases of tuberculosis in rural Ireland many years back as a public health doctor. Then it was a dreaded disease, consumption, with an enormous stigma attached, resulting in isolation and even condemnation. While some things have improved, such as the availability of antimicrobial chemotherapy, tuberculosis remains a global challenge and the most vulnerable and deprived are at greatest risk.

Those in educational roles would do well to remind students of its global importance as well as its many protean manifestations, sometimes resulting in it going undiagnosed. Our daughter’s current bedtime reading is L. M. Montgomery’s *Ann of the Island* in which the tragic case of Ruby Gillis is graphically described, dying of consumption, not having the chance to marry her beloved Herb. In many ways, that and Bernard Dixon’s imagery help remind us all of this great scourge in a more real way than the descriptions in textbooks or journals.

Hilary Humphreys
The Royal College of Surgeons in Ireland and Beaumont Hospital
Dublin, Ireland.

Corrections

In the May 2015 *Microbe*, p. 201, in the profile of Jennifer Glass, at the bottom of column 1, “Geoffery” should read “Geoffrey.” On p. 202, column 2, line 2, after Jennifer Glass, Bradley Tebo should be included as a co-chair of the “Metals and Microbes” symposium from the 2014 ASM General Meeting. *Microbe* regrets the errors.
Competitive Science: Is Competition Ruining Science?

Science has always been competitive, and despite recognition of the benefits of cooperation, the struggle for funding and jobs has made science more competitive than ever.

Ferric C. Fang and Arturo Casadevall

Science would be ruined if (like sports) it were to put competition above everything else.

— Benoit Mandelbrot

In the winner-take-all economics of science, scientists compete for priority, the recognition that they are the first to make a discovery, conferring prestige that, in turn, can lead to employment, funding, prizes, and membership in honorific societies. It is often taken for granted that this competitiveness is beneficial because it provides incentives for individuals to excel. It has also suggested that scientific rivalries can provide a corrective for confirmation bias, the tendency to favor evidence that supports one’s preexisting beliefs. Thus, in theory, competition may help to protect science from stagnation and dogma.

Not all historians of science view competition in such a uniformly favorable light. More recently, focus group discussions confirm that competition discourages sharing and may even lead some scientists to sabotage competitors, perform biased peer review, and engage in questionable research practices. Moreover, some scientific leaders decry the detrimental effects of hypercompetition, warning that it may be driving some young people, particularly women, away from careers in science.

Further, a relationship between competition for funding and scientific misconduct is increasingly recognized, with the important caveat that most scientists maintain their integrity despite difficult circumstances. Many scientists note that the “publish or perish” culture of contemporary science can foster bias in the scientific literature. Large surveys of science faculty in the United States show a significant association between pressure to obtain external funding and soft money salary support with questionable research practices and neglectful or careless behavior.

Competition is not required for seminal discoveries. Even the classic examples of scientific competition may be misleading. Darwin and Russell, for example, developed their theories of evolution by natural selection independently. When Russell sent a manuscript describing his ideas to Darwin, the latter hastily prepared a paper to be presented simultaneously to the Linnean Society of London, an action that in itself acknowledged the contributions of Russell. To his credit, Russell never contested the priority and greater depth and influence of Darwin’s work.

And what of the argument that competition reduces the danger of confirmation bias? While it is true that competing scientists are less likely to be invested in corroborating a theory, fierce competition might actually reinforce confirmation bias by encouraging scientists to dig in their heels and defend their positions rather than lose face. Collaboration with others who do not precisely share your views might be a more effective safeguard against confirmation bias.

Although transformative discoveries leading to entirely new fields can occur in the absence of competition, such discoveries can stimulate competing efforts to build upon that finding. Once goals are clearly defined, scientists recognize that achieving the goals can lead to rewards and that the first to solve the next problem will reap the greatest reward.

An example is the discovery that heredity is transmitted by DNA. Initial speculation as to the chemical nature of genes was restricted by technological limitations. Key research on the transforming principle came from a laboratory interested in understanding the relationship between different bacterial strains in the hope of developing better therapies and vaccines. DNA was thus linked to heredity, but several more years passed before the race began, with participants including Crick, Wilkins, Franklin, Chargaff, Pauling, and Watson. In the end, Watson and Crick won that race, and their elucidation of the DNA structure led to new fields and new competitions.

Few Nobel Laureates had that prize in mind when they made their award-winning discoveries, and most recipients received ample recognition long before Stockholm called.
Competition probably works best when goals are clearly defined and a field is technologically ready. A good example is the Human Genome Project, in which competition between publicly and commercially supported teams led to success years ahead of schedule. However, competition by itself cannot lead to progress if the goals are too ambitious, as demonstrated by many unclaimed prizes in science and technology.

With the shortcomings of competition becoming more evident, collaboration appears to be in ascendency along with the need for diverse research approaches and transdisciplinary teams to address complex problems. However, a greater emphasis on “team science” will require a radical reconsideration of how scientists are organized, supported, and rewarded.

By channeling research efforts along defined paths, competition may constrain the creativity required for transformative breakthroughs. At its best, science is a creative process on par with art, music, and literature, and involving imagination, intuition, synthesis, and aesthetic.

According to psychologists, intense competition and stress can stifle creativity, which flourishes when an individual is allowed to pursue a subject about which he or she cares passionately, and in an environment that feels more like play than work. “When creativity is under the gun, it usually ends up getting killed,” says psychologist Teresa Amabile of the Harvard Business School in Boston, who also warns that the detrimental effects of competition on creativity may affect men and women differently. Does cooperation work? In contrast to competition, there are many examples of the benefits of cooperation and collaboration, according to author Steven Johnson, who analyzed 135 major innovations in science and technology from the 19th and 20th centuries. “Openness and connectivity may, in the end, be more valuable to innovation than purely competitive mechanisms,” he concluded. “Good ideas... want to complete each other as much as they want to compete.”

The history of science repeatedly shows that important scientific findings arise from unfettered exploration, the passion of individual scientists to understand a problem, and research environments that foster interaction. Although our current scientific enterprise could hardly be less conducive to creativity, these principles come as no surprise to working scientists.

There remains a role for competition in science. Competition appears to work best for algorithmic rather than heuristic tasks that require great creativity. Thus, defining specific goals that are technologically feasible can help to advance particular projects. However, most science today would benefit from a radically different structure that promotes cooperation, collaboration, and creativity.

Useful measures may include changing the criteria for professional advancement, with an emphasis on common rather than individual goals and a reduced emphasis on publication in prestigious venues. Unselfish scientific acts such as mentoring and making useful reagents and information available to the community should be recognized, along with more effective policing of scientists who behave selfishly. Another strategy to reduce the detrimental effects of competition is for competing groups to cooperate by publishing their findings at the same time so as to not “scoop” one another.

A major change in the economic structure of science with a renewed national investment in research and development is required to alleviate hypercompetition for grants and jobs. In this regard, a system that funds people instead of projects may be more rational. A greater emphasis should be placed on open-ended investigator-initiated research and less on targeted programs. Institutions should reduce their dependence on soft money to provide researchers with more stable salary support. Larger research teams to increase numbers of senior scientist positions can enhance intragroup networking and ameliorate competition among trainees.

Scientists today work in an environment of relentless stress, time pressure, and insecurity, factors that are counterproductive to good science. However, creativity thrives on freedom and interactivity. It is time to apply these principles to reform the scientific enterprise itself.

Editors’ note: The full version of this article, including references and additional text, was published in *Infection and Immunity* in January 2015 (83:1220–1233).

Ferric C. Fang, Departments of Laboratory Medicine and Microbiology, University of Washington School of Medicine, Seattle, is Editor in Chief of *Infection and Immunity*, and Arturo Casadevall, Johns Hopkins Bloomberg School of Public Health, Baltimore, Md., is Editor in Chief of *mBio.*
Current Topics

RESEARCH ADVANCES

Ebola Outbreak Spurred Sequencing and Diagnostic Efforts

Jeffrey L. Fox

Despite difficult conditions throughout West Africa during the height of the Ebola outbreak, the European and American teams conducting diagnostic procedures during the crisis provided an important and effective component of the broader clinical and public health interventions that brought the outbreak under control.

The bulk of that diagnostic testing relied on RT-PCR. At first, most of the clinical specimens were sent to Europe or the United States (US) for analysis. However, as the outbreak expanded and the numbers of specimens grew exponentially, arrangements were made to conduct those diagnostic analyses locally, often in makeshift laboratories—“‘hot labs’ under tin roofs,” as one on-site participant noted. Indeed, specimens were “hot,” meaning biologically dangerous, and ambient temperatures were plenty hot, playing havoc with instruments designed for use in air-conditioned settings.

A European consortium sent two mobile laboratory units to Africa, with one of them deployed to Guinea in March 2014, according to Stephan Guenther of the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany. At first, local officials “built a nice tent for us,” he says. Later, a “more stable structure” was made available for ongoing diagnostic work, some of it done inside glove boxes—a challenging undertaking because of the high numbers of samples being analyzed.

While PCR analysis played a lead role during the outbreak, genomic sequencing also was brought into play—not to diagnose individual cases but to determine whether and in what ways the Ebola virus might be changing during the course of the outbreak, according to Jeffrey Kugelman of the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick in Frederick, Md. At first sequencing analysis was done with samples sent to U.S. and European labs. However, because shipping logistics were cumbersome and speedier results were deemed critical, a good part of that work shifted to Africa, he says.

The early focus of genomic sequencing was to determine whether changes in viral sequence might lead the virus to be resistant to experimental therapeutics, Kugelman says. Now sequencing data also are being scrutinized to determine whether genomic changes might affect diagnostic probes or, more broadly, might help to explain other features of the outbreak.

Other, simpler rapid diagnostics are already available or soon will be. Early this year, Food and Drug Administration (FDA) officials issued an emergency use authorization to Corgenix of Broomfield, Colo., for its ReEBOV antigen rapid test for detecting antibodies to Ebola in blood samples. “This is a preliminary assay for testing patients to support triage,” says Robert Cross of the University of Texas Medical Branch, Galveston, who is part of a larger consortium helping to develop and evaluate such tests. The results from such testing need to be “validated with PCR,” he adds. Unlike PCR, however, the antigen tests are easy to use, yield results within minutes, and hold up well to heat and other adverse conditions.

Another whole-blood test system being developed and which is funded by the National Institute of Allergy and Infectious Disease, like PCR, amplifies nucleic acid to detect the Ebola virus, in...
Ultrasmall Bacteria: 150 Could Fit inside an E. coli Cell

Carol Potera

New three-dimensional images show bacteria so tiny that 150 of them could fit into a single Escherichia coli cell. “These ultrasmall bacteria are a subset of microbial life on Earth that we know almost nothing about,” says Jill Banfield at the University of California, Berkeley. She and her colleagues used two- and three-dimensional cryogenic transmission electron microscopy to gather information about the cell walls, morphology, and volume of these ultrasmall bacteria. Details appeared 27 February 2015 in Nature Communications (doi:10.1038/ncomms7372).

The ultrasmall bacteria were discovered in groundwater filtered through standard 0.2-µm filters and collected at a Department of Energy research site in Rifle, Colo. The cells have an average volume of 0.009 µm³, an average length of 323 nm, and an average width of 242 nm, according to Banfield and her collaborators. Electron tomograms reveal periodic spirals within each cell that likely consist of DNA, an average 42 ribosomes per cell, and pili along the cell surface of various lengths and thicknesses that probably enable these cells to attach to other microorganisms. Meanwhile, bacteriophages are visible along the surfaces of some of these ultrasmall bacterial cells.

Some of these miniaturized microbial cells are dumbbell-shaped, suggesting the cells are dividing or budding, according to Banfield. Their metabolic options appear to be limited—for example, the cells undergo no significant tricarboxylic acid cycle and lack components of the electron transport chain, making it likely that they scavenge building blocks from other microbes. “We have no clues to the functions of 50% of their genes,” she says.

Metagenomic and other DNA-based analysis match the ultrasmall bacteria to the WWE3, OP11, and OD1 candidate phyla, whose other members are found in diverse environments, including hot springs, permafrost, mines, oceans, peat bogs, and subsurface ecosystems. In a forthcoming report, Banfield and her colleagues estimate that bacterial members of those phyla are “part of a larger group of small organisms that may comprise up to 15% of all bacteria on Earth,” she says. Investigations of these enigmatic microbes could lead to insights about how such microbial communities affect water, climate, and other ecosystems.

The miniaturized size of these newly recognized bacteria may help them “to attain a greater surface-to-volume ratio, which may be handy for taking up scarce resources in oligotrophic environments,” says Moselio Schaechter, visiting scholar at the University of California, San Diego, and distinguished professor emeritus of Tufts University in Boston, Mass.

Because these ultrasmall bacteria live under fairly stable conditions, “they need not carry extra genes for adap-
minitopic

Developments Involving Antibiotic Resistance

Recent developments involving antibiotic resistance include:

- Three widely used herbicides—dicamba (Kamba), 2,4-dichlorophenoxyacetic acid (2,4-D), and glyphosate (Roundup)—induce changed responses to antibiotics in *Escherichia coli* and *Salmonella enterica* serovar Typhimurium, according to Jack Heinemann of the University of Canterbury in Christchurch, New Zealand, and his collaborators. Resistance sometimes increases but other times decreases for antibiotics from five different classes, they report. Details appeared 24 March 2015 in *mBio* (doi:10.1128/mBio.00009–15).
- Exposing *E. coli* or *Klebsiella pneumoniae* to the biocide triclosan leads to mutants with resistances to other biocides and also to antibiotics, and to a variety of other metabolic and fitness changes, according to Maria Teresa Coque of CIBER Epidemiología y Salud Pública in Madrid, Spain, and her collaborators at several institutions in Spain, England, and Italy. Details appeared 30 March 2015 in *Antimicrobial Agents and Chemotherapy* (doi:10.1128/AAC.00187–15).
- Use of antimicrobials in agriculture is expected to rise by 67% by 2030, and nearly to double in Brazil, Russia, India, China, and South Africa, according to Ramanan Laxminarayan of the Princeton Environmental Institute in Princeton, N.J., and his collaborators. “[Antibiotic] effectiveness—and the lives of millions of people around the world—are now in danger due to the increasing global problem of antibiotic resistance,” he says. Details appeared March 19, 2015 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1503141112).
- Scientists should reduce antibiotic use in experiments as a way to reduce selection pressures leading to drug resistance, says Laura Bowater of the University of East Anglia in the United Kingdom. “It is timely for us to consider other options,” she says. Details appeared March 19, 2015 in the *Journal of Antimicrobial Chemotherapy* (doi:10.1093/jac/dkv071).
- Chlorine in water treatment facilities might be modifying antibiotics within the mix at such facilities, yielding novel compounds that lead to development of antibiotic-resistant microbes in the environment, according to Olya Keen at the University of North Carolina, Charlotte, and her collaborators. They presented their findings during the national meeting of the American Chemical Society, held in Denver, Colo., last March.

**ASM MEETINGS AND CONFERENCES**

**Taking a Closer Look at Metabolic Changes when Hosts and Pathogens Meet**

Jeffrey L. Fox

One fresh approach to countering pathogens, including those that might be weaponized, calls for focusing on how they change their hosts as well as how their hosts might change them metabolically, according to several experts who spoke during the 2015 ASM Biodefense and Emerging Diseases Meeting, held last February in Washington, D.C. Here are several brief accounts of how investigators are probing these interactions in their search for a better understanding of particular pathogens and the search for new countermeasures to hold them in check.

Although “fastidious” when growing on plates, *Francisella tularensis* is a “robust” gram-negative bacterial pathogen in nature, according to Alain Charbit of INSERM in Paris, France. The cytosol of host cells, mainly macrophages, serves as its “sanctuary,” he says. Some 400 genes, accounting for about 20% of the genome, “participate” in its activities as a pathogen.
Once ensconced in the cytosol of a host macrophage, this pathogen comes to depend on its immediate surroundings for key nutrients, including several amino acids, Charbit continues. Because these building blocks of proteins are critical for the survival of this bacterial pathogen, the transporter proteins that play a critical role in supplying those amino acids are de facto virulence factors. The genes encoding them are available in ample supply, falling into 26 families and encoding more than 90 such proteins, more than half of which are needed to ensure virulence, he says. “They do peculiar things.”

For example, without its transporter for asparagine, intracellular *Francisella tularensis* cells become auxotrophic for this amino acid, Charbit says. One reason that this newfound dependence is peculiar is that the cells still carry genes conferring the capacity to make that amino acid. “We don’t know yet why it becomes a functional auxotroph,” he says. “It’s perfectly capable of making these amino acids.”

Viruses also perturb and reorder the metabolic activities of the cells that they infect, says Josh Munger of the University of Rochester in Rochester, N.Y., referring in particular to human cytomegalovirus (hCMV). Soon after it infects a target mammalian cell, central energy-generating metabolic pathways, including the tricarboxylic acid (TCA) cycle, glycolysis, and the pentose-phosphate shunt, undergo dramatic changes. The TCA cycle, for instance, accelerates fatty acid biosynthesis by as much as 50-fold, while glycolysis is up-regulated a less-dramatic but still significant two-fold, and pentose-phosphate activities decrease, he says. In much the same spirit, John Wikswo of Vanderbilt University in Nashville, Tenn., and his collaborators are applying cholera toxins to neuronal cells, looking for signals as to how such agents affect target cells, he says. “We want to find early signals to anticipate something bad will happen and, ideally, learn how to block it.”

By working with cells and tissues, it becomes possible to expect “fast read-outs” of metabolic activity following insults from pathogens or toxins, according to Wikswo. One analytic approach he is pursuing is to adapt ion mobility mass spectrometry to the analysis of metabolites that appear in cells following exposure to pathogens. “We can use this approach to study mechanism of action,” he says. Even if the toxin or pathogen is an unknown or unidentified agent, this approach could provide a window into how it is acting and perhaps into how its damaging effects might be blocked.
NEW IN ASM JOURNALS

**Agent from Soil Microbe Blocks B. subtilis from Forming Biofilms, Spores**

David C. Holzman

A soil microbe-produced antimicrobial agent blocks *Bacillus subtilis* cells from forming biofilms or spores without killing these bacteria, according to Elizabeth A. Shank of the University of North Carolina, Chapel Hill, Matthew Powers, an undergraduate student in her lab, and their collaborators. The active agent, 2,4-diacetylphloroglucinol (DAPG), is produced by the soil bacterial species *Pseudomonas protegens*, has both antibacterial and antifungal activities, but at subinhibitory levels affects development and physiological responses of *B. subtilis* cells without killing them, they point out. Details appeared 30 March 2015 in the *Journal of Bacteriology* (doi:10.1128/JB.02535–14).

Some compounds that soil bacteria secrete act subtly—for example, as signals to alter the behavior of other nearby organisms, according to Shank. In this case, DAPG blocks formation of biofilms, which are notoriously resistant to conventional antibiotics. For instance, biofilms are problematic in dental and health settings, causing plaque on teeth and giving rise to persistent infections that are seeded via biofilms on medical implants, such as catheters and indwelling devices such as joint prostheses. They also interfere with industrial processes—for example, by clogging or corroding pipes, and by instigating corrosion on ships.

Their experimental approach, which entailed use of a reporter strain that fluoresces when specific biofilm genes are blocked, could be adapted to help in identifying other compounds that inhibit biofilms, according to Shank. Such compounds, or the bacteria that produce them, could be used either as chemical tools or as probiotics, respectively, she suggests. Additionally, because both these bacteria associate with plant roots, “understanding how they interact with each other using these secreted compounds may be important for creating healthy microbial soil communities for plants to grow in,” she says.

“It is intriguing to see how a compound produced by a gram-negative species can encroach on the differentiation of a gram-positive bacterium,” says Akos T. Kovacs of the Friedrich Schiller University in Jena, Germany. “The fact that compounds affect development in other species independently of their antimicrobial impact is fascinating, and suggests a need to reevaluate our thinking on compounds used to inhibit microbial growth.”

The research raises another important scientific question, Kovacs continues. “What is the evolutionary advantage for a bacterium in responding to these compounds by altering biofilm formation?” he asks. While more powerful signals, including toxins and antibiotics, produced by many bacteria are better known and more widely appreciated, this territory in which more subtle signals exert their influences remains relatively poorly mapped, he notes. However, Shank’s findings suggest that the importance of these more subtle chemical signals may be far greater than is apparent after a first glance.

“It is about time that everyone realized that bacteria in nature grow as communities and rely on close intercellular signaling with small molecules at low concentrations,” says Julian Davies at the University of British Columbia in Vancouver, British Columbia, Canada. “Also, that antibiotics and chemical signals are the same thing, the difference is in concentration. In addition, this work strengthens the notion that small molecules at low—or, signaling—concentrations probably control our resident microbiota.”

David C. Holzman is the Microbe Journal Highlights Editor.

**MINITOPIC**

**Pathogens of Crops, Crop Resistance Mechanisms—an Update**

Recent developments involving pathogens affecting crops include:

- A newly recognized DNA virus in the genus mastrevirus, being called switchgrass mosaic-associated virus 1, was found infecting switchgrass but might also infect grains such as corn and wheat, according to Carl Bradley of the University of Illinois, Urbana-Champaign, Bright Agindotan, now of Montana State University, Bozeman, and their collaborators. Details appeared May 2015 in *Archives of Virology* (doi:10.1007/s00705–015–2367–5).

- A gene encoding a bacterial receptor was transferred from *Arabidopsis thaliana*, a dicotyledonous plant, to the monocot wheat, enabling it to trigger broad resistance responses to bacterial diseases, according to Henk-jan Schoonbeek and Christopher Ridout of the John Innes Centre in Norwich, United Kingdom, and their collaborators. Details appeared April 2015 in the *New Phytologist* (doi:10.1111/nph.13356).

- An elicin response gene, ELR, which encodes a receptor-like protein in the South American plant *Solanum microdontum*—a wild relative of potato—when transferred to cultivated potato plants enhances resistance to *Phytophthora infestans*, the pathogen responsible for potato blight, according to Vivianne Vleeshouwers at the Wageningen University and Research Centre in Wageningen, Netherlands, and her collaborators. Details appeared March 30, 2015, in *Nature Plants* (doi:10.1038/nplants.2015.34).
Nitrogenase, the core component of the nitrogen cycle, was likely operating long before oxygen became available in the global atmosphere some 2.3 to 2.4 billion years ago, according to Eva E. Stüeken and Roger Buick of the University of Washington in Seattle and their collaborators there and the University of Johannesburg in South Africa. Their findings suggest that this complex, molybdenum-containing enzyme is one of the oldest on the planet. Moreover, they raise the possibility that “life in the Archaean could have been more abundant with a greater biomass than previously suspected,” Buick says. Details appeared 16 February 2015 in Nature (doi:10.1038/nature14180).

These conclusions are based in part on analyses of rock samples containing isotopes of nitrogen from sediments deposited 2.75 to 3.2 billion years ago along continental margins in South Africa and northwestern Australia. The findings indicate that nitrogen-fixing organisms were using nitrogenase to fix atmospheric nitrogen long before the rise of oxygen in the atmosphere. This very early evolution of nitrogenase, enabling bacteria to fix nitrogen might also have averted the “nitrogen crisis” that some researchers say might have otherwise occurred during the Archaean or early Paleoproterozoic period, an event that would have set back evolution considerably.

Nitrogen is an essential ingredient in a variety of biologically important molecules, including proteins, DNA, and RNA. Today 80% of the nitrogen of our planet resides in the atmosphere, according to Buick. Nitrogenase arose “3.2 billion years ago,” he says, “before there was any evidence for oxidative weathering of sulfide minerals on land, the main source for molybdenum now. We infer that there was a small hydrothermal source, as there is now, from low temperature springs on mid-ocean ridge flanks, [accounting for] about 13% of the total molybdenum supply to the oceans.”

Buick and his collaborators “make a good case that biological nitrogen fixation was a very early development—the isotope data seem compelling,” says Chris McKay at NASA Ames Research Center in Moffett Field, Calif. “This implies that nitrogen fixation arose before the great oxidation event and the rise of oxygen in the atmosphere.” If correct, those findings “could explain why nitrogen fixation is sensitive to oxygen,” he adds. “In fact, the data appear to be consistent with nitrogen fixation going back to the beginning of the sedimentary record.”

The long-held view about nitrogen is that the biological demand for fixed nitrogen before the rise of oxygen in the atmosphere was so modest that it could be satisfied by drawing nitrogen from abiotic sources. In other words, without oxygen, the demand for nitrogen via fixation was negligible. “For nitrogen fixation to be present at very early times suggests that the total productivity of the biosphere was higher than previously thought and required more fixed nitrogen than could be provided by abiotic sources,” McKay says.

Barry E. DiGregorio is a freelance writer in San Diego, Calif., and Gonzalo Ballon-Landa report that the treatment eliminated multidrug-resistant organisms both in a patient’s gastrointestinal tract, and at several other body sites—a novel finding. “Intriguingly, we found that by letting the normal bacteria replenish his gastrointestinal tract, the resistant bacteria, which had plagued him up to that point, disappeared from his body,” says Crum-Cianflone. During the next two years, until the patient died, the C. difficile never returned, and only once did resistant bacteria—methicillin-resistant Staphylococcus aureus—recolonize. “Patients in long-term facilities receive numerous antibiotics that almost invariably result in both colonization and infections from multidrug-resistant organisms, in the end with bacteria resistant to all antibiotics,” says Ballon-Landa. “This paper indicates that replenishing the normal gut flora and keeping these patients off antibiotics can result in the disappearance of multidrug-resistant organisms from the patients’ bodies and thus potentially save their lives.”

Barry E. DiGregorio
crude oil with metabolic evidence confirming its potential for bioremediating both marine and terrestrial BP contaminated ecosystems. “This systemic integrated research approach provides advanced knowledge to bridge the gaps between in vitro and in vivo and between in situ and ex situ, which hinder efforts toward practical bioremediation,” says Cerniglia. “With the knowledge about the oil-degrading enzymes and their function in *Mycobacterium vanbaalenii* PYR-1, a further understanding of the physiology, biochemistry, and genetics of oil component degradation would enhance efforts in environmental cleanup,” the team concludes.


NEW IN ASM JOURNALS

**Inappropriate Antibiotic Use Continues Despite CDC Campaign**

The Centers for Disease Control and Prevention has promoted the appropriate use of antibiotics since 1995, when it initiated the National Campaign for Appropriate Antibiotic Use in the Community. Now Kari Mergenhagen of the VA of Western New York Healthcare System Infectious Disease Department, et al. find poor compliance with the campaign. More than three-quarters of patients were prescribed an antibiotic, and fully 64.3% of 1,662 patients at her institution who were seen in the study received therapy deemed inappropriate under Campaign criteria, says Mergenhagen. In particular, outpatients treated for respiratory infections received inappropriate treatment. The authors conclude, “This article provides evidence the current efforts are insufficient to curtail inappropriate antibiotic use.”


NEW IN ASM JOURNALS

**Phage Spread Antibiotic Resistance**

Strategies to combat antimicrobial resistance have enjoyed only limited success, and many questions linger as to how and when resistance transfer occurs. Now Friederike Hilbert of the University of Veterinary Medicine, Vienna, Austria, et al. show that phage randomly isolated from chicken purchased from supermarkets, street markets, and butcher shops transferred resistance to tetracycline, ampicillin, kanamycin, chloramphenicol, and to extended-spectrum beta-lactam antibiotics. Nearly half of the 50 chicken samples contained viruses capable of transferring resistance among different bacteria, and different species, says Hilbert. “Our work suggests that such transfer could spread antibiotic resistance in environments such as food production units and hospitals and clinics.”


NEW IN ASM JOURNALS

**Leaf-Cutter Ants’ Fungus Gardens Show Biotechnological Potential**

Leaf-cutter ants cultivate gardens of the obligate mutualistic basidiomycete fungus *Leucoagaricus gongylophorius* on fresh vegetal matter. Mauricio Bacci, Jr. of the Sao Paolo State University, Brazil, et al., show that the fungus garden is a biphasic solid-state bioreactor with peripheral and core sectors working synergistically to convert plant matter to monosaccharides and polyols, which the ants subsequently consume. They note the system’s efficiency: the microbes, which account for 4% of the fungus garden’s biomass, convert the plant matter into monosaccharides and polyols, which are completely consumed by the resident ants and microbes. “However,” they write, “when consumption was inhibited through laboratory manipulation, most of the plant polysaccharides were degraded, products rapidly accumulated, and yields could be preferentially switched between polyols and monosaccharides.” The latter feature, they suggest, might be used in biotechnology.

Microbes Help To Drive Global Carbon Cycling and Climate Change

Although global balancing of carbon dioxide is more complex, in the short term some marine microbes trap it, while soil microorganisms release it.

Shannon Weiman

Microbes are integral to global carbon cycling, directly and indirectly affecting atmospheric carbon levels that, in turn, further drive global climate change, according to an array of researchers who spoke in Boston during the 2014 ASM General Meeting. In most cases, photosynthetic microbes remove carbon dioxide from the atmosphere, converting this gas into biomass or helping plants to do so. However, heterotrophic microbes in soils and in the sea can help to produce greenhouse gases by decomposing organic matter. The balance between these opposing processes determines net carbon flux, and varies from one ecosystem to another and with climate conditions such as temperature. Microbial responses are a key but only partly understood component of carbon flux for the planet.

“Although microorganisms catalyze most biosphere processes related to fluxes of greenhouse gases, little is known about the microbial role in regulating future climate change,” says Jizhong Zhou of the University of Oklahoma in Norman, who spoke during the session, “Microbial Interactions in a Changing Climate.” In trying to unravel this mystery, he and other researchers are studying diverse terrestrial and aquatic ecosystems, stretching from the poles to the equator, in an effort to determine where microbes mitigate or exacerbate climate change, and how changing climate conditions influence their roles in global carbon cycling. In many cases, they report, microorganisms act as buffers against increasing atmospheric carbon dioxide levels, slowing but not altogether halting climate change.

Marine Microbes Near Antarctica Sequester Carbon Dioxide from the Atmosphere

Oceans, particularly in polar regions, support huge numbers of photosynthetic microorganisms that sequester large volumes of carbon from the atmosphere, according to Patricia Yager of the University of Georgia, who spoke in the same session as Zhou. “High-latitude oceans are capable of taking up massive amounts of atmospheric carbon dioxide due to high biological productivity and low temperature,” she says. While oceans sequestered approximately 25% of human-generated carbon dioxide since 1960, the Southern Ocean is responsible for absorbing the lion’s share, about 40% of this total, mostly by physical processes, she points out.

Yager and her collaborators study polynyas, areas of open ocean that are surrounded by sea ice that provide habitats for phytoplankton blooms (Fig. 1). These blooms act as efficient biological pumps, fixing carbon dioxide into

SUMMARY

➤ Microorganisms can act as buffers against increasing atmospheric carbon dioxide levels, slowing but not altogether halting climate change.
➤ Oceans sequester approximately 25% of human-generated carbon dioxide through physiochemical and biological processes, with the Southern Ocean responsible for absorbing the lion’s share of this total.
➤ On land, permafrost is by far the largest store of carbon compounds, where the initial impact of thawing is to release carbon dioxide via microbial decomposition.
➤ Prairie grasslands are another essential piece of the carbon cycle puzzle and here, too, initial releases of carbon tend to be followed by periods of stability, leaving uncertainties about long-term effects.
biomass, which then sinks to the ocean floor to form long-term carbon stores, she says. “Polynyas are often areas of high biological production during summer, facilitating substantial carbon dioxide exchange with the atmosphere.” For instance, the Amundsen Sea Polynya (ASP) has the highest algal productivity in all the Southern Ocean. It removed, on average, 18 mmol of carbon per m² per day from the atmosphere during the 2010–2011 season, with some high productivity areas doubling that rate. This high carbon flux is 50% larger than that reported during peak blooms in the well-studied Ross Sea, and well over those of most continental shelves around the world.

“As the most biologically productive polynya per unit area, the ASP provides a window to investigate and better understand the sensitivities and vulnerability of biogeochemical cycling in the coastal regions of Antarctica,” says Yager. Polynyas are highly climate sensitive, and have been undergoing seasonal shifts due to global warming that influence sea ice coverage and therefore carbon flux. Higher temperatures, as well as changes in seasonal winds and wind-driven ocean circulation, are causing polynyas to open up earlier in the season, potentially allowing for more productive blooms. “Earlier opening of the ASP could extend the productive season and enhance the magnitude of the phytoplankton bloom, if enough light and iron are available,” she says. “In this event, the ASP could become a greater carbon sink in the near future.”

Indeed, for the past three decades, the Southern Ocean consistently removed increasing amounts of carbon from the atmosphere, acting as a biological buffer to help mitigate climate change, according to Yager. However, with increasingly rapid environmental changes in polar regions, it is difficult to predict whether these microbial communities in polynyas will continue to offset anthropogenic carbon dioxide production, she warns.
Arctic Sea Ice Provides a Habitat for Microbes that Remove Carbon from the Atmosphere

Ocean waters in the Arctic also harbor aquatic microbes that remove carbon from the atmosphere, according to Antje Boetius of the Max Planck Institute for Marine Microbiology in Bremen, Germany, who spoke during the plenary session, “Global Change Microbiology: Anthropogenic Pressures and Microbial Responses.” Boetius studies aquatic algae that grow under sea ice, investigating how retreating ice may influence carbon fluxes in these microbial communities.

In the past, thick perennial ice prevented sunlight from penetrating into these below-ice ecosystems, according to Boetius. However, thinning ice layers, and increasing melt-pond coverage provide environments where photosynthetic algae can grow, converting carbon dioxide into biomass. “As a consequence of Arctic warming, primary productivity in and under the ice may be boosted by higher light transmission through thinning sea ice, and the increase in melt pond coverage during summer,” she says.

In particular, the diatom *Melosira arctica* claims responsibility for an estimated 45% of Arctic primary productivity under ice around the North Pole, forming filaments up to several meters long that anchor to the underside of ice floes. “When the ice gets thinner than 1 meter and they get enough light, *M. arctica* start growing and in a short period of time build up a large biomass below the ice,” says Mar Fernandez, who works with Boetius. These microbial tendrils can cover up to 40 to 80% of the underside of undisturbed ice floes.

*M. arctica* also acts as a long-term carbon sink when ice melts, leaving these filaments with no means of flotation. The sub-ice algal aggregates sink rapidly to the sea floor, sequestering substantial amounts of carbon to the benthos layer along the ocean bottom. These algal deposits cover up to 10% of the floor of the central Arctic basin, accounting for 85% of total organic carbon export to the ocean bottom within Arctic ecosystems in 2012, according to Fernandez. With global warming trends, these numbers are also on the rise. “The high amounts of ice algal carbon observed at the sea floor in summer 2012 (median 9 g carbon per square meter) was 10 times higher than total carbon export fluxes measured in the Central Arctic in summer 2007 (of less than 0.1 g),” she says.

Similar phenomena are under way within other specific Arctic ecosystems. “Increases in carbon export flux to the seafloor due to sea-ice retreat were previously observed in the Laptev Sea,” says Fernandez. However, the capacity of these Arctic microbes to buffer atmospheric carbon levels may be short-lived as ice floes recede. Indeed, summer sea ice is predicted to disappear by 2050, leaving *M. arctica* without a substrate on which to grow. “In the long term, when the Arctic crosses its tipping point and summer sea-ice disappears, their life cycle will not be sustainable anymore and they will disappear, resulting in a substantial decrease in sea-ice related productivity and ice-algal export to the benthos,” she says.

Tropical River Plumes also Capture Atmospheric Carbon

Tropical oceans also host microbes that sequester carbon from the atmosphere, mitigating climate change, according to Yager. In these otherwise nutrient-poor waters, microbes depend on nutrients delivered by large rivers such as the Amazon, she says. “The nutrients delivered by these river plumes contribute to enhanced primary production in the ocean, and the minerals enhance the sinking flux of this new production, resulting in carbon sequestration.” The plume of the Amazon River is the largest on Earth, affecting ecosystem productivity and biogeochemistry thousands of miles offshore, almost all the way to Africa, she says (Fig. 2).

Microbial communities shift in composition and function throughout the plume of the Amazon, responding mainly to changes in nutrient availability and salinity, according to Yager. In terms of fixing large amounts of carbon from the atmosphere, the phytoplankton that blooms in water with medium salinity and low nitrogen play an important role, she says. “Plume waters create conditions favorable for carbon and nitrogen fixation, and blooms of diatoms and their diazotrophic cyanobacterial symbionts have been credited with significant carbon dioxide uptake from the atmosphere.” She and her collaborators estimate that the plume sequesters $2.4 \times 10^{12}$ mol (or $29 \times 10^{12}$ g) of carbon per year. The carbon-fixing diatoms within that plume then sink rapidly to the ocean floor, exporting carbon at rates comparable to other notable carbon sinks located...
at higher latitudes in the southeastern Atlantic and Southern Oceans.

This highly efficient system for handling carbon depends on partnerships among the diatoms *Hemiaulus hauckii* and *Rhizosolenia clevei*, and their nitrogen-fixing cyanobacterial symbionts, *Richelia intracellularis*. The abundance of these species in plume waters correlates with ecosystem productivity and carbon fixation, Yager finds. "The nitrogen-depleted region in the outer plume may be an ecological niche for diazotrophs and their diatom symbionts," she says. "The diazotroph *R. intracellularis* fixes nitrogen to support its diatom host *Hemiaulus* spp. or *Rhizosolenia* spp., which may drive carbon sequestration in this region. Such symbiotic relationships between marine planktonic microbes are rather new to the scientists, and highlight how biodiversity and biological interaction play a role in ecosystem function."

Other tropical rivers, including the Congo, Nile, and those that feed the China Sea, also exhibit these diatom diazatroph-driven, carbon-sequestration systems, driving important ecosystems that mitigate climate change. However, these waterborne microbial communities are highly sensitive to local environmental conditions. "The enhancement of nitrogen fixation and consequent carbon sequestration by tropical rivers appears to be a global phenomenon that is
likely to be influenced by anthropogenic activity and climate change,” Yager says. Changing precipitation patterns and changes in levels of fertilizers from changing land use along these river basins could affect salinity, nutrient, and oxygen availability in these plume-fed waters, altering microbial community structures and potentially disrupting their carbon-cycling functions.

**Elevated Microbial Decomposition within Melting Permafrost Releases Greenhouse Gases**

On the terrestrial side of polar regions, melting of one-time permafrost tracts also may prove important for microbial carbon cycling. Permafrost is by far the largest terrestrial store of carbon compounds, according to Janet Jansson of Lawrence Berkeley National Laboratory in Berkeley, California, who spoke during the same 2014 ASM General Meeting session as did Zhou and Yager. Permafrost underlies one-fourth of the Earth’s terrestrial surface, and it can be several hundred meters deep, she says. These layers contain “huge amounts of buried, ancient organic carbon.”

While frozen these soil carbon stores are relatively inert, according to Jansson. However, as temperatures increase throughout the polar regions, these frozen soil layers are thawing, allowing microbes to decompose organic matter that is stored within them. This permafrost thaw also alters largely dormant microbial community structures within those layers, accelerating biogeochemical processes such as respiration, fermentation, and methanogenesis, converting soil carbon into greenhouse gases such as carbon dioxide and methane, she says. “During transition from frozen to a thawed state, there are rapid shifts in many microbial phylogenetic and functional gene abundances and pathways... multiple genes involved in cycling of carbon and nitrogen shift rapidly during thaw.” This reviving microbial activity in thawing permafrost tends to accelerate climate change by releasing carbon dioxide and methane into the atmosphere from the vast amounts of stored organic carbon compounds in those soils.

How these soil-bound microbial communities will respond in the long term to such thawing as vegetation and other environmental factors shift in response to climate change is unknown, and global feedback mechanisms could tip the balance of carbon flux either way, according to Jansson. “Eventually, microbial activities will dictate whether permafrost environments will be a net source or sink of greenhouse gases in the coming decades, and whether large-scale feedbacks to regional and global climate will develop because of increased (greenhouse gas) emissions,” she says.

**Native Prairie Grasslands—Microbes Stabilize Carbon Flux**

Prairie grasslands are another essential piece of the carbon cycle puzzle, accounting for 31–39% of soil carbon stores and covering 27% of the American landscape, says David Myrold, of Oregon State University in Corvallis, who spoke during the same session as Zhou. Both Myrold and Zhou study soil microbes in these regions, which can release large amounts of carbon dioxide from soil carbon stores. “Soil respiration is the second largest carbon flux on earth... returning 75–80 gigatons of carbon to the atmosphere per year,” says Zhou.

Changing precipitation patterns can affect microbial communities in prairie soils, Myrold says. “Climate change is predicted to alter precipitation patterns globally, which may have major effects on the carbon balance of grassland ecosystems. Resulting shifts in microbial carbon cycling activity could affect soil carbon storage. “We quantified rainfall-driven dynamics of microbial processes that affect soil carbon loss and retention... measuring microbial respiration, biomass, organic matter decomposition potential, and community composition,” Myrold continues, referring to long-term experiments on swaths of prairie soil microbial communities. When precipitation is less frequent but overall equivalent over the longer term, respiration and carbon dioxide production in those communities also drop, revealing a negative feedback mechanism to conserve soil carbon stores. “Soil carbon loss may be reduced or compensated for via different mechanisms at varying time scales.”

Already by 1999, Zhou began exposing microbial communities within native prairie grasslands in Oklahoma to elevated temperatures and atmospheric carbon dioxide levels. Both warming and elevated carbon dioxide significantly alter the phylogenetic and functional structure of
these communities, stimulating microbial respiration, he finds. Microbes actively release labile carbon stores—plant matter that is easily decomposed such as starch, cellulose, and chitin. However, when confronted with other types of carbon compounds, microbial activity remains unchanged, he says. “Differentially stimulating genes for degrading labile but not recalcitrant carbon could be important in maintaining long-term stability and storage of ecosystem carbon.”

Despite increases in microbial respiration, net carbon flux within this ecosystem remains constant, again thanks to microbes, Zhou finds. Warming and elevated carbon dioxide also stimulate microbial genes involved in fixing nitrogen and using phosphorous, both of which support plant growth that removes carbon from the atmosphere, offsetting increases in microbial respiration, he says. “Warming enhances genes in nutrient-cycling processes such as denitrification, nitrogen fixation, nitrification, nitrogen mineralization and phosphorous utilization... such changes may have significant impacts on soil carbon and nitrogen dynamics.”

Thus, microbial responses to climate change in prairie grasslands exert stabilizing effects on carbon cycling, acting as a buffer for climate change, Zhou says. Without these microbe-mediated mechanisms and feedbacks, more soil carbon would have been lost to the atmosphere. “Although microorganisms play critical roles in ecosystem functioning and regulating the responses of ecosystems to climate change, they are rarely explicitly considered in carbon-climate models.”

The roles that microorganisms play in ecosystem carbon cycling dynamics are significant on a global scale, and should be taken into account when estimating the effects of climate change. Although some of these findings are provisional, in many cases, microbial adaptations to changing environmental conditions point to their important role as efficient biological carbon pumps, mediating biogeochemical processes and stabilizing feedback mechanisms that help to delay global climate change.
Redefining Virulence of Bacterial Pathogens

Measuring bacterial gene expression and metabolism during infections provides a more comprehensive view of virulence in action

Harry Mobley

Investigators identifying virulence genes at first did so by examining transposon mutants or individual gene mutations. Mutants of bacterial pathogens were then assessed in animals, whose symptoms mimicked human disease. Later, genome-wide screens were developed whereby genes and proteins that influence virulence could be identified, including via signature-tagged mutagenesis (STM), in vivo expression technology (IVET), and in vivo-induced antigen technology (IVIAT). Investigators then began to use RT-PCR to measure expression of individual genes, including within infected tissues. Microarray technology enables us to estimate global gene expression under defined culture conditions such as nitrogen limitation, oxygenation, and osmotic stress.

These efforts led to our conventional view of microbial virulence, with its focus on adhesins, iron acquisition, toxins, secretion, and motility, as well as on bacteria with genes such as those on horizontally transferred pathogenicity-associated islands that are not found in commensal strains. Now, however, we also must consider what metabolic pathways are in play when microbial pathogens infect their hosts. What’s for dinner? How are these bacteria metabolizing available molecules to colonize a particular body site? Which import and export systems are active during infection?

Because mutations in these systems should reduce fitness, we should measure transcription under relevant conditions. For pathogens that infect humans, those conditions require analysis during infections whenever possible. This approach rests on the hypothesis that virulence is the sum of required metabolic pathways, traditional virulence determinants, upregulated transport systems, and other functions.

Importance of Measuring Bacterial Gene Expression in Hosts

In the last decade, investigators used microarrays to assess gene expression of pathogens, including Borrelia burgdorferi, Burkholderia pseudomallei, Campylobacter jejuni, Escherichia coli, Helicobacter pylori, Listeria monocytogenes, Mycobacterium spp., Mycoplasma hypopneumoniae, Streptococcus pyogenes, and Vibrio cholerae, infecting mice, rats, gerbils, rabbit ileal loops, hamsters, and pigs. For example, my collaborators and I measured in vivo gene expression of uropathogenic E. coli (UPEC) collected directly from urine of mice using this model for ascending urinary tract infection (UTI). We also studied transcriptomes of E. coli directly from the urine of patients with complicated UTI and in otherwise healthy women with uncomplicated UTI using RNA-Seq. Overall, only a few research groups have measured genome-wide gene expression during human infections with V. cholerae, Pseudomonas aeruginosa, M. tuberculosis, and E. coli.

SUMMARY

➤ With many virulence genes already identified, it is time to consider metabolic pathways and export-import systems that also contribute to the infectious process.
➤ Among several types of Escherichia coli pathogens, the versatile uropathogenic strains provide good examples for redefining virulence to capture its metabolic dimensions.
➤ In some cases, metabolic pathways may be missing or inactive without affecting virulence; similarly, expression of specific virulence genes may vary from one strain to another without affecting the overall course of an infection.
➤ Specific host settings can determine which bacterial virulence genes are expressed.
Taken together, these techniques provide a broad view of virulence. Close examination of individual genes and operons, along with complementation experiments, provide more detailed assessments. Further, we know that additional factors are required for colonizing and infecting humans or other host species. Critically, the metabolism of pathogens needs to match available nutrients and oxygen levels for them to thrive in hosts. Thus, the contribution of bacterial metabolism must be added to the study of virulence to craft a complete picture.

One Species Helps Redefine Bacterial Virulence

To redefine the meaning of virulence, let us look carefully at one versatile pathogen, E. coli, whose many pathotypes developed through countless transfers of foreign DNA into commensal strains via conjugation, transduction, and transformation. For example, enterohemorrhagic E. coli received the Shiga toxin gene via transduction as well as its pathogenicity island carrying the locus of enterocyte effacement (LEE) probably following conjugation.

It is but one among other E. coli intestinal and extraintestinal pathotypes. For example, this species causes diarrhea in at least six different ways, including by enterotoxigenic, enteropathogenic, enterohemorrhagic, enteroaggregative, enteroinvasive, and diffuse-adherent E. coli. Each has its own mechanism of pathogenesis. Beyond the intestinal tract, extraintestinal E. coli causes urinary tract infection and meningitis in humans, and lung infection in birds.

Consider one of these pathotypes, uropathogenic E. coli, which causes about 80% of ascending urinary tract infections in otherwise healthy women. Infections typically start when feces contaminate the periurethral area, from which bacteria ascend into the bladder, causing cystitis (Fig. 1A). From there, bacteria ascend the ureters toward the kidneys. On a human scale, this journey entails about a 45,000-foot (15,000-meter) climb in 2 hours on a path covered in mucus.

We can visualize some of these steps in mice that we inoculate with E. coli CFT073 expressing a flagellin-lux fusion (Fig. 1B). When the flagellin gene (fliC) is transcribed, we see a burst of light. From the back of the animal, we can see that these bacteria ascend the ureters to the kidneys within two hours. In some cases, these bacteria cross epithelial and endothelial barriers into the bloodstream.

These bacteria have up to 12 types of fimbrial adhesins. The most notable is P fimbriae, which binds the P blood group antigen expressed on the surface of kidney epithelial cells. Six O serotypes, which are antigenic variants of lipopolysaccharide (LPS), cause three-fourths of infections. These strains, which synthesize capsules (K antigen) that evoke serum resistance, are chemotactic and motile. They also make many iron and heme receptors, and exotoxins such as hemolysin, cytotoxic necrotizing factor, cytolethal distending toxin, and several autotransported proteases.
Using Pathogenicity Islands when Defining Virulence

Another way to define UPEC strains involves analyzing how they acquired pathogenicity islands. For example, we hybridized genomic DNA from fecal-commensal strains, cystitis strains, and pyelonephritis (ones infecting kidneys) strains to a microarray of *E. coli* CFT073, which is the most cited prototype UPEC strain, from gene 1 through gene 5364. This analysis reveals that *E. coli* CFT073 contains significant stretches of DNA that are not present in other strains, particularly fecal strains (Fig. 2A). Indeed CFT073 carries 13 pathogenicity islands ranging from 30 to 100 kb that were inserted around the chromosome and account for about 12% of the genome (Fig. 2B). These accessories enable *E. coli* to move into the bladder.

From a survey of those genes from 315 strains, including fecal, cystitis, and pyelonephritis strains, we note that as *E. coli* moves higher up the urinary tract, it is considered more virulent and more likely to have those genes. For example, about 70% of pyelonephritis strains have particular fimbriae called Auf (another UPEC fimbria) found in fewer than 20% of fecal strains. This relationship holds up for other fimbriae, toxins, and iron acquisition systems (Fig. 2C).

Other Factors that Help To Define Bacterial Virulence

Of course, these virulence genes are not all the factors required for bacteria to infect a host. Metabolic cycles, including glycolysis, gluconeogenesis, the tricarboxylic acid (TCA) cycle, pentose phosphate pathway, and the Entner-Duodoroff pathway, may all play a part. The bacteria that colonize the urinary tract rely on nutrients in that environment. What is available to them?

To test whether *E. coli* needs all those metabolic pathways, we introduced single mutations that specifically knock out each of these cycles, inoculated the mutants into the bladders of mice, and then measured the number of bacteria after 48 hours. Mutants with defects in the TCA cycle or gluconeogenesis had impaired fitness during UTI.

However, when the glycolytic, pentose phosphate, and Entner-Duodoroff pathways are knocked out, the mutants colonize the urinary tract just fine. Peptide transporters such as DppA and OppA are induced in urine, and required for infection. From these findings, we surmise that amino acids and peptides are the primary carbon source for *E. coli* infecting the urinary tract. Presumably peptides are taken up, converted into amino acids, and then oxaloacetate enters the TCA cycle, boosting oxidative phosphorylation and gluconeogenesis to make glucose, which is not usually present in the urinary tract. The fact that bacteria need only a few of their major metabolic pathways during infections is surprising.

Measuring Bacterial Gene Expression during Infections

To learn what else *E. coli* does in vivo, we looked at the transcriptome several ways—collecting bacteria from the urine of infected CBA mice or from women with complicated urinary tract infections. Bacterial RNA was isolated, converted into cDNA, and then hybridized to the *E. coli* CFT073 microarray (Fig. 3). For eight patients, “red” signifies that a virulence gene is expressed, while “black” means that it is not expressed or absent. Virulence factor genes include those for fimbria, toxins, iron acquisition, capsule, metabolism genes, and transporters.

The relative expression during human UTI versus murine UTI yields a good correlation (r = 0.589; P < 0.0001), especially for iron acquisition proteins, which are highly expressed in both mice and humans. In humans, however, fimbrial genes are not well expressed by bacteria collected in urine. Although informative, these comparisons are not ideal because the eight strains from the urology clinic were compared to the genome of another strain, *E. coli* CFT073.

Next, we asked what *E. coli* does by collecting urine specimens from 86 women with relatively uncomplicated infections. The urine from about half the women contained more than 10⁵ CFU/ml, with 38 of the samples positive for *E. coli*. We isolated those strains for genomic sequencing, while subjecting RNA from five strains to sequencing to determine their transcriptomes. By phylogenetic analysis, these strains were UPEC strains in the B2 and D phylogenetic groups, lining up nicely with prototype UPEC strains CFT073, 536, UTI89 (all B2) and UMN26 (D).

Also consistent with UPEC strains, the genome sizes were 8–15% larger than *E. coli* K12, suggesting that they contain several pathogenicity islands.
In terms of expression of traditional virulence factor genes, one strain expressed high levels of type 1 fimbriae and lower levels of P fimbriae and FIC fimbriae (Fig. 4). Iron acquisition proteins also are highly expressed because urine is iron-limiting. Toxin genes such as hemolysin and CNF, proteases, and flagella are expressed weakly. However, in another strain, the type 1 fimbriae are very poorly expressed but the P fimbria gene is expressed well and iron acquisition genes are more highly expressed than they are in the first strain.
Expression of type 1 fimbriae is very important because, although essential in mice, it is variably expressed during human UTI. The promoter for type 1 fimbriae resides on an invertible element, which recombinases can turn on and off, meaning it is phase variable. Using an invertible element assay, 6 of 21 strains from urine of women with UTI were on, while in 12 strains the whole population was off, and in 3 strains parts of the population were on and other parts off.

**Comparative Transcriptomics Reveal Host-Induced Bacterial Genes**

Using comparative transcriptomics, we compared the expression or abundance of RNA in urine samples from UTI patients to the same bacteria cultured from urine from age-matched, healthy volunteers. If we look at specific transcripts, we can identify some that are highly expressed in the host but not in urine. What are the specific genes that are expressed only while bacteria are in the host? Averaging data for five strains, host-induced genes were those encoding import systems for sulphonate, nickel, phosphonate, taurine, and potassium, and copper efflux, osmoprotection, and colanic acid synthesis. These are representative of UTI-specific genes.

Thus, some host factor(s) turns particular genes on, while the bacteria continue to synthesize many other virulence factors. If we compare samples from UTI patients to bacteria growing in vitro in urine collected from healthy volunteers,
we see that the host-induced genes are, on average, 32-fold more highly expressed.

For each one of those genes, we sought to verify their involvement in virulence by making clean mutations, mixing mutants with wild-type CFT073, inoculating those bacteria into mice, and then culturing samples from the bladder and kidneys to calculate the competitive index (mutant CFU/wild type CFU). For copper export, the wild type outcompetes mutants lacking *cus* genes. Moreover, these bacteria appear to consume ethanolamine from host epithelial cells. Also within the human urinary tract, the bacteria also take up nickel, sulfonate, potassium, phosphonate, and taurine while expelling copper ions.

### Different Bacterial Genes Are Required for Different Host Settings

When cystitis progresses to pyelonephritis, *E. coli* can break through tubules and capillaries in the kidney to enter the bloodstream. To identify genes supporting this development of bacteremia, we used transposon-directed insertion site sequencing, inoculating 360,000 transposon mutants simultaneously into the tail vein of a mouse. We then recovered bacteria from the spleen and sequenced their genomic DNA to see which mutants are underrepresented in the bloodstream to identify those genes that provide a fitness advantage during bloodstream infection.

For example, in the inoculum, the sensitivity to antimicrobial peptide (*sap*) operon gene had 622 insertions, while samples from the spleen contained only 91 insertions, equivalent to a fitness factor of 6.8. We investigated other genes with fitness factors 2 standard deviations above the mean. The top 11 mutants included genes for producing poly N-acetyl glucosamine, an iron receptor, a zinc peptidase, a type IV pilus, oligopeptide uptake, resistance to antimicrobial peptides, and two serine proteases. Wild-type *E. coli*
Transcript levels during human UTI with strain HM27 (A) and HM69 (B).
significantly outcompeted all these mutants during bacteremia.

Taken together, virulence can be redefined as the sum of classical virulence factors, requisite metabolic pathways, and key import and export pumps. Measuring gene expression in vivo is critical to defining virulence of bacterial pathogens.

Harry Mobley is Frederick G. Novy Distinguished University Professor and Chair of the Department of Microbiology and Immunology at the University of Michigan Medical School, Ann Arbor.

Suggested Reading


Making the Microbiology Lecture a Passionate Performance, with Stories and Songs

To teach more effectively, microbiologists or other specialists need to convey their passion for their chosen subject matter

Sheldon Campbell

Many of you reading this feature spend roughly half your waking hours in some form of professional activity. Why did you choose that particular activity? For the money? Because your parents or a teacher made you? Many of you might answer “because it’s important.” However, that answer is not very particular. We live in a complex world in which a capable person can pursue any number of career paths. Why pursue the particular path that you do? Why, among the vast array of potential occupations, are you interested in microbiology?

I suspect that at some point most of us fell in love with, if not our specific area of study or practice, at least some closely related area in microbiology. I know that I did. I recall the exact moment that, sitting in a session on the African trypanosome at a cell biology meeting in St. Louis, I fell for the study of microbes.

One “Catches” a Love for Science

As a microbiologist, I would say that a love for science or for some particular specialty is not a skill to be learned but a contagion to be caught. That love requires an infected source, a susceptible host, and an efficient means of transmission.

Practicing and teaching microbiologists are the infected source. Some of our students are susceptible hosts. And lectures, embattled though they may be in current educational practice, can be an efficient means of transmission. Lecturers who incorporate interactive elements into their lectures, who develop a personal style and pay attention to the performance aspects of lectures, and who aspire to inspire as well as inform, can transmit not only knowledge and skills, but also their love of the field to their students.

To be competent, a lecturer needs to know the material, select relevant information for the audience at hand, organize that information in a way that illuminates underlying concepts, and communicate it clearly. Mastering those components is not only a good starting point, it is most of the work of teaching.

However, a lecture is both a cognitive exercise in communicating knowledge, skills, and attitudes, and also a performance, one that should capture and hold the attention of the audience, which might be jaded and oversaturated with other information. Like the science itself, the performance of the lecture is a learnable skill. That skill, the skill of performing to engage the audience, is something that separates a competent lecture, which merely informs, from an outstanding lecture, which both informs and inspires.

Challenges for readers: When did you “fall in love” with the area you currently work or teach in? Describe the moment.

SUMMARY

➤ Showing passion for microbiology makes one a more effective teacher of this subject.
➤ Lectures are both a cognitive exercise in communicating knowledge and skills, and a performance aimed at capturing the attention of the audience.
➤ Lecturers can better engage students by posing questions for them to answer as pairs or small teams.
➤ Other elements of style, including songs, that encourage students to talk over subject matter, help to convey both the substance and the excitement of microbiology.
Engaging Students with Stories

Lectures need not be merely one-way broadcasts. In his book, *Peer Instruction: A User’s Manual*, physicist Eric Mazur describes “ConcepTests,” which are simple questions that are introduced during lectures as interactive tools for engaging students. This procedure is easily adapted for use in microbiology courses.

In outline, its use is as follows:
- pose question
- allow students to commit to an answer (1 minute)
- allow students to discuss and convince a neighbor of that answer (1 minute)
- show of hands for each answer (30 seconds)
- discussion (1 minute)

During a 1-hour lecture, dealing with two to four questions is about right. According to Mazur and his collaborators, this approach to teaching has a positive impact on students learning physics. Posing interactive questions markedly alters the dynamics of lecture classrooms, requiring students to apply what they hear, and then testing and correcting their skills. Moreover, anyone who was at risk for dozing wakes up.

The peer instruction component—having students confer in pairs—is essential for this method to work. The dynamics force each student to engage with every question posed during the lecture instead of allowing the most vocal students to carry the class.

Although this feature appears in a magazine, not in a lecture hall, readers might approximate the Mazur approach that I am describing by responding to each of the questions contained in this article. Then, try to contrast that experience with mere reading.

Challenges for readers: Find a time within the next day to tell someone else about the moment you fell in love with the work that you are doing now. Ask them to reciprocate.

Songs: Personalizing Your Teaching

Bob Dylan, the Grateful Dead, and Peter, Paul, and Mary each have performed the traditional ballad “Pretty Peggy-O,” but you could never mistake one performer’s version of that song for another. An essential component of engaging performers is that each develops a distinct style. A lecturer should do the same thing.

However, striving for a distinctive style goes against the grain of our prevailing scientific culture. Scientific procedures are supposed to be reproducible when moved from one laboratory to another. Similarly, in terms of style, scientists are expected to carry themselves as calm and objective. This manner, however appropriate to science, is wrong for moving lecturing style from merely competent to excellent or, to use terminology familiar to NIH-funded faculty, from excellent, meaning the grant application probably will not be funded, to outstanding, which means it has a realistic chance.

Performers of the stage and screen, however, strive not to be merely reproducible but to be unique and to speak with vivid and personal voices. Observe outstanding teachers, and learn from them. Two of my mentors in medical teaching exemplify the art of personalizing the lecture. Frank Bia, an amateur historian, incorporated historical anecdotes and analogies into every lecture he gave. Marie Landry, whose specialty is viral disease, uses personal stories and pictures describing her personal encounters or those that her friends and especially her children have had with viruses.

I sing about microbiology to my medical students, residents, and even to scientists attending national meetings. After attending folk-music camp years ago, I learned to play the guitar and began writing and adapting traditional songs, which I love, to microbiological themes—for example, “Oh, give me a home, where the parasites roam, where the worms play in cheerful delight. . .”

The core songs I use in my medical-school course are reworked from folk songs, and they include titles such as “Home in the Gut,” adapted from “Home on the Range”; “Fungi, Come Again No More,” adapted from “Hard Times”; “When the Ticks Go Marching In,” from “When the Saints Go Marching In”; and “What Shall We Do with the Infected Patient,” from “What Do You Do with a Drunken Sailor.” Folk songs are ideal for the purpose because so many students know the tunes already and because the songs contain refrains that students can join in singing. Consider, for example:

Tis the song of the immunocompromised
Fungi, fungi, come again no more
Too many antibiotics and other drugs I’ve seen
Oh, fungi, come again no more!
When these words are sung to the tune of Stephen Foster’s “Hard Times,” they make a point in a more memorable way than does a conventional summary slide.

My songwriting approach, of course, is not generalizable; not everyone can sing and play guitar. (In some circles, skeptics question whether I can.) However, almost all of us have some passion or interest outside science to bring into the classroom. Introducing such external interests into lectures serves three ends: it makes a lecturer’s performance more passionate, it connects with students on noncognitive levels, and it connects science with other activities from everyday life.

Challenges for readers: Write down a subject outside science or medicine about which you are passionate. Think of a way to connect that passion to your professional interest. Find a way to tell someone about it.

Encourage Students to Hear It, Write It, Say It

I owe this idea to Carolyn Hovde Bohach, who described it during her 2005 ASM Carski Lecture. Instead of presenting an intellectual framework for education, she presented 17 suggestions, describing teaching as an activity where the details matter and where good execution is essential. Her suggestion number 12 called for encouraging students to “Hear It, Write It, Say It!”

This advice impressed me. If a teacher can get students to think and talk about microbiology outside the classroom, it can have a powerful impact on their learning. Based on her advice, I created examples that differ slightly from her original concept. Instead of using her comments on a summary slide, I ask “Who you gonna call?” I ask students to talk about what they learned.

Use talking points like the following: Did you know that there are two major causes of fatigue, stiff neck, fever, and sweating, but only one of them is meningitis? You know, I’m feeling dizzy and disoriented around you. It’s probably your fabulousness, but in case it’s meningitis, you might want to make yourself eligible for meningococcal prophylaxis.

Yes, these talking points are lame. Relentless lameness is a style all its own. However, this exercise in translating learning objectives into everyday conversations is valuable because it forces the learner to re-examine information, putting otherwise esoteric concepts into new and more familiar contexts.

Another trick is to anthropomorphize microbes. For malaria gametocytes, the *Anopheles* mosquito serves much the same purpose that the back seat of an old car serves for some adolescents, providing a place to do one’s business without the parents—the other bloodstream stages of the parasite. While we discourage anthropomorphizing microorganisms in a research context, where this bias can be problematic, it can provide a “hook” for learning new information. In other words, creating recognizable stories from microbial lives is a valuable and effective teaching tool.

Passion in the Lecture Hall

Biomedical science deals with the essential mechanisms of life and death—the machinery of birth and love and music and all human activity. This machinery has astonishing complexity, baroque intricacy, and fundamental importance. Thus, the practice of medicine is among the most compelling activities of our society, as measured by its prevalence in so many TV dramatic series.

Why, then, are our publications and spoken presentations so dry? The reasons are twofold. The culture of scientific objectivity, utterly necessary for the careful study of nature, can be antithetical to passionate expression. The second reason, though, is perhaps more tractable and systemic. Scientists do not make expressing the joy of our work part of our work.

It is insufficient simply to be passionate about what we do. We must show it, especially when communicating with students, but even with our peers and our nonscientist acquaintances. We must aim not merely to inform, but to inspire. When speaking about your profession, you are speaking about what you spend...
most of your waking hours doing, what you devote your life to doing. Expressing passion for that subject matter to your students will raise your teaching from being adequate to outstanding.

*Challenges for readers:* Describe your professional activities in a sentence or two. Then, complete the following sentence: This stuff is wonderful (note, I did *not* say important) because... Incorporate these comments into your next talk, and find a way to talk about it to a nonscientist.

It is insufficient merely to feel the passion for what you teach. You have to communicate it, conveying not only information but attitude, not only scientific knowledge but our appreciation of the deep wonders of nature and the joy of discovery. We have to become more intentional and more expressive in the words we use to describe science. Elegant is overused. Is the biology peculiar? Baroque? Astonishing? Delicate? Bizarre?

Find drama in the stories of nature, and use your voice to emphasize it. Create suspense; ask questions, delay answering them. Listen to great speakers and actors and comedians. They change volume, change pace, use dramatic pauses. For performers, energy is a magical word. Use different voices—deep and dramatic, high and squeaky—for describing different concepts and different organisms. Throw yourself into the lecture, and use your body to illustrate concepts. Lecturing should operate at more than simply cognitive levels. Recognize and harness the value of nonverbal communication.

Be vulnerable. It is amazing what questions students will ask when you remind them that ignorance is a lifelong condition, and that you still think that it is fun to learn new things.

Above all, be passionate about your material. Honor the fact that every fact conveyed in a lecture is based on something someone thought was interesting enough to spend years studying. Organize lectures not only for conceptual coherence but also for drama. Above all, enjoy the process, and expect your students to do the same.

Sheldon Campbell is an Associate Professor in the Department of Laboratory Medicine, Yale School of Medicine, New Haven, Conn., and Clinical Pathologist, VA Connecticut Healthcare.

**Suggested Reading**

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ASM Meetings and Conferences

ASM Microbe 2016: Explore the Complete Spectrum of Microbial Sciences. Learn cutting-edge science and stay current at ASM Microbe 2016 (16–20 June, Boston, Mass.)—an inaugural event integrating ASM’s General Meeting and ICAAC to showcase the best of the microbial sciences. It is the only meeting in the field offering the opportunity to explore the complete spectrum of microbiology, from basic science to translational and clinical application. Attend this meeting to benefit from all of the high-quality programming of the General Meeting and ICAAC, and take advantage of targeted interdisciplinary sessions, topic-based networking opportunities, track-specific lounges, and more. For more information on this unmatched event, visit www.asm.org/microbe2016.

ICAAC/ICC 2015: Register Today for the Best Rate. Time is running out to register for the joint ICAAC/ICC 2015 meeting (17–21 September, San Diego, Calif.) with the best rate. Secure your seat before 6 August 2015 and save! Building on a rich history of debuting major advances in drug development and infectious disease research, this meeting will be 2015’s principal meeting for clinical microbiologists, infectious disease physicians, researchers, and pharmacists to attend to better improve the diagnosis, prevention, and treatment of infectious diseases around the globe. For more information and to register, visit www.icaac.org/icaac-icc.

2016 ASM Biodefense and Emerging Diseases Research Meeting: Save the Date. Mark your calendar for the 2016 ASM Biodefense and Emerging Diseases Research Meeting (8–10 February, Arlington, Va.). Recognizing that emerging infectious diseases serve as a paradigm for handling the public threat of bioterrorism, this event brings together individuals carrying out the research to defend against the growing threat of bioterrorism, as well as the decision makers shaping the future biodefense research agenda. For more information on this meeting, visit www.asm.org/biodefense2016.

Upcoming ASM Conferences. ASM conferences address the needs of the diverse scientific interests of microbiologists by providing a forum for international groups of scientists, ranging from 100 to 400 participants, to discuss their specific area of concentration. Mark your calendar for these upcoming ASM conferences. For more information, visit www.asm.org/conferences.

- ASM Conference on Pseudomonas 2015 (8–12 September, Washington, D.C.)
- ASM Conference on Rapid Next-Generation Sequencing and Bioinformatic Pipelines for Enhanced Molecular Epidemiologic Investigation of Pathogens (24–27 September, Washington, D.C.)
- 7th ASM Conference on Biofilms (24–29 October, Chicago, Ill.)
- 4th ASM-ESCMID Conference on Methicillin-Resistant Staphylococci in Animals: Veterinary and Public Health Implications (2–5 November, Chicago, Ill.)
ASM Public Affairs

ASM Comments on Select Agent Regulations

In April, ASM submitted two letters regarding the Select Agent Regulations (SAR). The first addressed the biennial review from the Centers for Disease Control and Prevention and the Department of Agriculture Animal and Plant Health Inspection Services (APHIS). ASM agreed with the proposal to remove two agents, Coxiella burnetii and Rickettsia prowazekii, from the HHS Select Agents and Toxins list and four biological agents from the Overlap Select Agents and Toxins list maintained jointly by The U.S. Department of Health and Human Services and APHIS (Bacillus anthracis Pasteur strain, Brucella abortus, Brucella melitensis, and Brucella suis). The letter is available at http://www.asm.org/index.php/public-policy/137-policy/documents/statements-and-testimony/93447-sar-4-15.

ASM also responded to a request for public comment from the Office of Science and Technology Policy on the impact that the SAR has had on science, technology, and national security, and on the benefits, costs, and limitations of the regulations. The letter addressed the burden of inventories, SAR record keeping, issues with inspections and a recommendation for a standing advisory committee of outside experts to advise the federal government on SAR regulations. The letter is available at http://www.asm.org/index.php/public-policy/137-policy/documents/statements-and-testimony/93444-sar-4-15.

Funding Recommendations to Congress

The ASM Public and Scientific Affairs Board (PSAB) released a booklet entitled "Federal Funding for FY 2016: Biomedical and Life Sciences Research," which is a compilation of ASM’s funding recommendations to Congress. Included in the booklet are funding recommendations for the National Institutes of Health, Food and Drug Administration, Department of Agriculture Research, Department of Energy, Office of Science, Centers for Disease Control and Prevention, National Science Foundation, and Department of Defense medical research programs. The booklet is available on the PSAB public affairs website at http://www.asm.org/images/PSAB/FedFunding-2016.pdf. For updates on the Fiscal Year 2016 appropriations process go to http://www.asm.org/ResearchFunding.

White House Releases National Action Plan to Combat Antibiotic-Resistant Bacteria

On 27 March, the White House released a plan that identifies critical actions to be taken by key Federal departments and agencies to combat the rise of antibiotic-resistant bacteria. The National Action Plan for Combating Antibiotic Resistant Bacteria outlines steps for implementing the National Strategy on Combating Antibiotic-Resistant Bacteria and addressing the policy recommendations of the President’s Council of Advisors on Science and Technology (PCAST) report on Combating Antibiotic Resistance. The National Action Plan outlines federal activities over the next five years to enhance domestic and international capacity to prevent and contain outbreaks of antibiotic-resistant infections; maintain the efficacy of current and new antibiotics; and develop and deploy next generation diagnostics, antibiotics, vaccines, and other therapeutics.


NIH RFI on Funding and Strategies to Improve Sustainability of Research

In April, the ASM Public and Scientific Affairs Board (PSAB) sent ASM members the National Institutes of Health (NIH) request for information (RFI) on optimizing funding policies and “other strategies to improve the impact and sustainability of the NIH-funded biomedical research enterprise.” The bulk e-mail let members know about the RFI and solicited responses to aid in the ASM response to NIH. The bulk e-mail is at http://www.asm.org/index.php/public-policy/98-policy/issues/93454-nih-rfi-4-15.

ASM Endorses Letter of Concern about Government Travel Restrictions

ASM signed onto a letter to Congress that expressed concern about the impact of Administration regulations and legislative initiatives related to government travel on the science and engineering enterprise and the pace of innovation. The letter highlights the importance of science and technology conferences for federal agencies scientists and urges Congress to work with agencies and the scientific community to ensure any further action does not

ASM Supports Reauthorization of the America COMPETES Act

In April ASM, as a member of the Coalition for National Science Funding (CNSF), endorsed a coalition letter sent to Lamar Smith (R-TX) chair and Eddie Bernice Johnson (D-TX), ranking member of the House Committee on Science, Space and Technology, supporting strong legislative language in the reauthorization of the America COMPETES Act. The letter raised concerns with the potential for individually authorized budget levels for National Science Foundation (NSF) directorates and stressed the importance of allowing the NSF the flexibility to fund grant proposals across the directorates in support of sound science and global competitiveness. The letter can be found on the Public Policy webpage at http://www.asm.org/images/PSAB/CNSF-HR-1806-2.pdf.

ASM Supports Funding for AFRI

ASM, a founding member of Supporters of Agricultural Research, signed on to a letter urging members of the House and Senate committee on appropriations, agriculture subcommittees, to fund the Agriculture and Food Research Initiative (AFRI) with at least $450 million in fiscal year 2016. AFRI is the Department of Agriculture’s competitive grants program and has been authorized at $700 million since its creation in 2008.

ASM Participates in White House Budget Call

On 16 April, ASM participated in a conference call with the White House Office of Science and Technology Policy (OSTP), Office of Management and Budget (OMB), and Office of Public Engagement and discussed the ongoing fiscal year (FY) 2016 budget process and specific research and development priorities. More information on the FY 2016 budget can be found http://www.asm.org/ResearchFunding.

ASM Participates in CDC Vaccine Ebola Prevention Study Call

On 24 March, ASM staff participated in the Centers for Disease Control and Prevention (CDC) conference call updating stakeholders on the Ebola prevention vaccine study in Sierra Leone. This was the fourth in this bimonthly “Partnering with the West African Community” Call Series, providing a brief update on the Ebola outbreak and response, a presentation on the Ebola Prevention Vaccine Study in Sierra Leone, and an explanation of CDC resources for members of the West African Community by Alison Albert, the lead health communication specialist for CDC’s Division of Bacterial Diseases in the National Center for Immunization and Respiratory Diseases and communications co-lead for the Ebola vaccine clinical trial in Sierra Leone. The transcript of these calls can be found at http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/communication-resources/west-african-communities-call.html.

Laboratory Practices Committee Prepares Duodenoscope Document

Recent reports of association of NDM-E. coli and CRE with duodeno- scope procedures prompted the ASM Public and Scientific Affairs Board (PSAB) Committee on Laboratory Practices to draft On the Question of Culturing of Duodenoscopes to address the unique challenges of pathogen identification in cases of infections associated with gastrointestinal endoscopy. The paper, which contains relevant links to Food and Drug administration and Centers for Disease Control and Prevention protocols, can be found at http://www.asm.org/index.php/public-policy-98-policy/issues/93456-ip-4-15.

PCAST Meeting

ASM staff attended the President’s Council of Advisors on Science and Technology (PCAST) meeting on 27 March at the National Academy of Sciences. The agenda included remarks from Office of Science and Technology Policy (OSTP) Director John Holdren and presentations from Agency representatives highlighting the programs they have implemented to combat antibiotic resistance. These representatives included Beth Bell, Director, Centers for Disease Control and Prevention National Center for Emerging and Zoonotic Infectious Diseases; Joe Larsen, Acting Deputy Director, Biomedical Advanced Research and Development Authority Division of Chemical, Biological, Radiological and Nuclear Medical Countermeasures; William Flynn, Deputy Director for Science Policy, Food and Drug Administration Center for Veterinary Medicine; and Steven Kappes, Deputy Administrator, Animal Production and Protection, Agricultural Research Service. The archived webcast and agenda of this meeting are at https://www.whitehouse.gov/administration/eop/ostp/pcast/meetings/past.

Education Board

New Fellowship Opportunity for Undergraduate STEM Faculty

Early-career (and future) undergraduate STEM educators are encouraged to apply for a 2015 ASM-LINK Undergraduate Faculty Research Initiative (UFRI) Fellowship. This new professional development resource trains STEM faculty to develop undergraduate research programs by initiating successful research partnerships. As part of the fellowship, ASM LINK will provide travel subsidies of up to $2,000 to (i) increase participation of undergraduate STEM educators at seven eligible ASM-sponsored research conferences, (ii) encourage networking and
collaborations with potential research partners, and (iii) access resources and mentoring to advance undergraduate research programs.

Fellowship applications are accepted on a rolling basis for each of the seven eligible ASM conferences. Deadlines are 13 and 27 July to be considered for UFRI Fellowships to two ASM topical meetings focused on *Pseudomonas* or Rapid Next-Generation Sequencing. To learn more, visit http://www.asmlink.org/ufri.

**ABRCMS 2015: Celebrating 15 Years of Encouraging Student Achievement in Science**

Registration is open for the 2015 Annual Biomedical Research Conference for Minority Students (ABRCMS), set for 11–14 November in Seattle, Wash. Join the conference as it celebrates 15 years of encouraging student achievement in science— and prepares for more exciting endeavors!

As a premier national gathering for undergraduates, ABRCMS is dedicated to guiding students in pursuit of advanced training in the biomedical and behavioral sciences, including science, technology, engineering, and mathematics. The conference is also committed to providing faculty mentors, advisors, and program leaders with resources for facilitating student success.

The ABRCMS focus is on supporting undergraduates, particularly those who are members of groups traditionally underserved in science, such as underrepresented minorities and persons with disabilities. The conference is also attended by many postbaccalaureates, graduate students, postdoctoral scientists, faculty, and administrators. All participants value the meeting’s information-rich lineup of workshops, scientific presentations, professional development opportunities, networking events, and more. In addition to marking its anniversary year, ABRCMS 2015 will feature plenary sessions and concurrent presentations by innovative investigators, mentors, and educators. This year’s plenary speakers include:

**Linda B. Buck,** Ph.D., Howard Hughes Medical Institute investigator and a researcher at the Fred Hutchinson Cancer Research Center. In 2004, Buck won a Nobel Prize for her work on odorant receptors and the organization of the olfactory system — the network responsible for our sense of smell.

**Jon R. Lorsch,** Ph.D., Director of the National Institute of General Medical Sciences at the National Institutes of Health. Lorsch leads the execution of the institute’s mission to promote advances in scientific research and biomedical workforce training.

**Patricia E. Molina,** M.D., Ph.D., Richard Ashman Professor and head of the Department of Physiology at the Louisiana State University Health Sciences Center, New Orleans. Molina is president of the American Physiological Society. Her research interests include the impact of chronic alcohol abuse on HIV/AIDS.

**David Quammen,** three-time recipient of the National Magazine Award. An author of 12 books, Quammen has written about the Ebola epidemic, the AIDS pandemic, and other zoonotic disease outbreaks for *Outside, National Geographic,* and other publications.

**Nontombi Naomi Tutu,** human rights activist, the daughter of Archbishop Desmond Tutu, and advocate for social justice. In her work promoting tolerance and inclusion, Tutu strives to bring different groups together to learn from each other, celebrate their differences, and acknowledge their shared humanity.

**Hannah Valantine,** M.D., Chief Officer for Scientific Workforce Diversity at the National Institutes of Health. A cardiologist with a proven record of implementing diversity initiatives in academic medicine, Valantine is charged with developing a vision and comprehensive strategy to expand recruitment and retention and promote inclusiveness and equity throughout the biomedical research enterprise.

Students (undergraduate through graduate levels) are invited to submit abstracts and travel award applications for the conference. Travel awards are also available to (i) postdoctoral scientists and faculty members who serve as ABRCMS onsite presentation judges and (ii) faculty who wish to establish research partnerships and advance undergraduate research programs. Deadlines are 1 September for the ASM LINK Undergraduate Faculty Research Initiative (UFRI) Fellowship, 11 September for ABRCMS Student Abstracts and Travel Awards, and 25 September for the ABRCMS Judges’ Travel Subsidy and the FASEB MARC Program Travel Award.

For submission criteria, registration information, or program and speaker updates, visit www.abrcms.org.

ABRCMS is managed by ASM and supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number T36GM073777.

**International Affairs**

**2015 Indo-US Professorship Grantees**

The ASM-IUSSTF Indo-US Professorship Program encourages scientific partnerships between the United States and India. Teaching Professors share their expertise through short courses with a practical component. Research Professors initiate projects that foster new scientific collaborations and technical training. From a strong pool of candidates, ASM and the Indo-US Science and Technology Forum selected the following grantees:

**Jayanthi Shastri,** T N Medical College & Nair Hospital, was awarded an Indo-US Teaching Professorship to deliver the course “Vector-Borne Diseases: Diagnosis, Prevention & Control” at the University of South Florida in Tampa, Fla., hosted by Cathy Pettii.

**Peter Uetz,** Virginia Commonwealth University, was awarded an Indo-US Teaching Professorship to de-
There are three physicians and six hospital beds per 10,000 Yemeni citizens. In contrast, the U.S. has 24 physicians and 30 hospital beds per 10,000 people. Those who can afford to do so travel outside the country for urgent medical procedures; however, roughly half the population lives in poverty. The recent military conflict has deteriorated health services even further.

Responding to these needs, ASM is supporting the efforts of the National Central Public Health Labs (NCPHL) Yemen to strengthen and expand clinical microbiological services, and by extension the country’s health system. ASM partnered with the NCPHL to provide professional development opportunities to NCPHL staff from regional labs throughout the country in early 2015. In cooperation with Manipal University in India, ASM sponsored six NCPHL microbiologists to receive training on PCR techniques in February 2015. At Manipal University’s Center for Virus Research (MCRV) participants improved their skills in areas such as extraction techniques, conventional and real-time PCR theory and practical application, and biosafety program management during hands-on exercises led by MCRV experts. Upon returning to Yemen, the travel grant recipients began training their coworkers.

In addition, 10 NCPHL staff participated in a two-week workshop addressing best practices for clinical diagnostics through ASM’s proven mentoring process in March 2015. The ASM Microbiology Mentoring Program aims to strengthen and expand clinical microbiological services through long term engagement of laboratory staff. The workshop, held at Jordan University for Science and Technology, was comprised of practical lab exercises and classroom sessions that trained participants to mentor their colleagues in conventional microbiology and quality and biorisk management. Following the training, the participants returned to their labs with plans to conduct assessments to identify gaps, and begin mentoring their coworkers in best practices, with the remote support of the ASM expert.

Despite the current political turmoil which poses significant challenges to their work, ASM looks forward to continued collaborations with the NCPHL-Yemen staff and hopes to further support their efforts through virtual consultations.

ASM Continues Collaborating with CDC-Guyana to Strengthen National STI Diagnostic Capacity

Since 2013, ASM has collaborated with the National Public Health Reference Laboratory (NPHRL) in Georgetown, Guyana, on developing a coordinated and quality-assured diagnostic network to combat the country’s high incidence of sexually transmitted infections (STIs). Over the past several years, ASM has led an STI needs assessment of the microbiology unit, identified four priority diseases (chlamydia, gonorrhea, hepatitis B, and syphilis) in Guyana, preselected and procured corresponding STI rapid diagnostic testing (RDT) kits, and designed a pilot implementation program for complete roll-out and scale-up of STI RDT kits slated to launch in Summer 2015.

To complement the in-country activities completed thus far and to promote the sustainability of the program, ASM also created an STI virtual training package for long-term use by laboratory personnel. This electronic training package consists of PowerPoint presentations and corresponding recorded lectures for each of the diseases and cover a variety of topics including disease overviews, alternative diagnostic methods, the use of rapid diagnostic testing kits in the laboratory setting,
and World Health Organization and Center for Disease Control and Prevention recommendations on diagnostic standards. All modules were sent to the NPHRL in electronic format and are currently being used by the microbiology unit at the NPHRL.

In the coming months, ASM will continue working closely with CDC and the NPHRL staff on implementing the STI RDT kit pilot and training program. An ASM consultant will travel to Georgetown to work with the NPHRL staff to confirm the specificity and sensitivity of the preselected testing kits and provide training on the testing kits to key laboratory staff. In addition, ASM plans to implement a training-of-trainers (TOT) program to promote sustainability of the STI diagnostics project in Guyana. The TOT will ensure that a group of laboratory managers maintains their skills and passes it along to mentees accurately.

Finally, ASM will assist with implementation of a quality assurance cycle for the RDT kits and administration of competency assessments for all trainees. This will ensure that the kits are utilized accurately, which will strengthen the impact of the program potentially also the incidence of chlamydia, gonorrhea, hepatitis B, and syphilis in Guyana. ASM looks forward to continued collaboration with SBS to increase biosafety/biosecurity awareness in India through targeted training programs. The success of the Biosafety Awareness Program underscores the power of sister society partnerships to promote international safe and secure microbiology.

Biosafety in a Time of Ebola: ASM Brings Egyptian Scientists to the African Biosafety Association Conference

ASM encouraged regional dialogue on biosafety by sponsoring seven Egyptian scientists and bringing an expert on Ebola and biorisk management to the African Biosafety Association’s (AfBsa) 4th Annual Biological Safety Conference in March 2015 in Casablanca, Morocco. Fifty scientists from 12 countries attended ASM’s preconference workshop on biorisk management in resource-constrained settings, which was led by an ASM expert consultant with on-the-ground experience managing Ebola biosafety systems in West Africa. The workshop focused on how to create a “culture of safety” as a laboratory manager, by understanding and motivating different personalities. It also resulted in a lively discussion on clinical containment strategies during the Ebola epidemic.

The sponsored Egyptian scientists spoke on topics as diverse as best practices for containing foot-and-mouth disease, effective waste management strategies at university hospital networks, the status of avian influenza research in Egypt, and the prevalence of antimicrobial resistance in Egyptian laboratory facilities. ASM will continue to provide training in Egypt this year by establishing BioResource Centers (BRCs) in Cairo and Alexandria. These BRCs, which are sustainable repositories of microbiology resources, will literally put Egyptian scientists on the “biosafety map” by allowing them to network with scientists at over 35 other BRCs around the world. BRCs and future AfBsa events hold great promise for increasing regional collaboration on biosafety and emerging diseases.

Branches: ASM Activities at the Local Level

ASM Student Chapter in Puerto Rico Hosts Award-Winning Documentary Microbirth

This month I have the pleasure of sharing with you a report on a very special activity organized and hosted by the ASM Student Chapter at the Inter American University of Puerto Rico, Metropolitan Campus, one of the many Student Chapters sponsored by the active Puerto Rico Branch. I hope that once you finish learning of this program and its success you too will be impressed with the high level of

ASM Partners with SBS in Biosafety Training Program in India

In March 2015, ASM and the Society for Biosafety-India (SBS) brought together 101 microbiologists from across India for a two-day Biosafety Awareness Programme at the National Institute of High Security Animal Diseases (NIHSAD) in Bhopal, India. These microbiologists hailed from veterinary and clinical institutions in 10 Indian states. During the workshop, participants were trained in basic biosafety, biosecurity, and dual use research topics using ASM’s Culture of Responsibility interactive video program. They then delved into specific biosafety and biosecurity topics, through sessions on India-specific biosafety regulations and safe operation of biosafety cabinets, and the pilot of modules from ASM’s new Pathogen Inventory Management course.

By providing small travel grants to 34 scientists from across India to attend the workshop, ASM and SBS were able to engage isolated scientists in the growing biosafety training network in India. ASM looks forward to continued collaboration with SBS to increase biosafety/biosecurity awareness in India through targeted training programs. The success of the Biosafety Awareness Program underscores the power of sister society partnerships to promote international safe and secure microbiology.
programming organized by these enthusiastic and dedicated students and become motivated to take advantage of the value that Chapters and Branches offer by attending your upcoming local Chapter and Branch activities, and perhaps by getting involved in the planning and implementation of such activities!

Michael Schmidt
Chair, Branch Organization Committee

On Friday, 21 February 2015, students from the Inter American University of Puerto Rico, Metropolitan Campus ASM Student Chapter, along with their mentor, Filipa Godoy-Vitorino, hosted the Puerto Rico premiere of the documentary, *Microbirth: the Microscopic Secrets of Delivery*. The event, jointly sponsored by the Inter American University of Puerto Rico, the Puerto Rico Society of Microbiologists (Puerto Rico Branch ASM), and the Bio-Nuclear of Puerto Rico, was fully organized by the students.

The documentary, which won first prize at the Prague Film Festival in 2014, explores the importance of the microbiome of infants in health and disease. The human microbiome—the aggregate of microorganisms that normally live in and on us (in humans, there are 10 times more microbial cells than human cells) —is becoming an increasingly important research area as science continues to uncover the extent to which microorganisms influence the essential functions of the human body. Focusing on the microbiome of infants, the film presents scientific evidence demonstrating that the passage of the baby through the birth canal of his/her mother, is essential for the introduction of beneficial bacteria that serve as the basis for the formation of the individual’s microbiome and will also facilitate the development of his/her immune system. The film goes on to discuss how modern practices of delivery, such as caesarean section, can interfere with critical biological processes, thereby increasing susceptibility to diseases such as asthma, diabetes type 1 and obesity.

The film screening was offered free of cost to Student Chapter members, Puerto Rico Branch (Puerto Rico Society of Microbiologists) members, and other interested local faculty, students, and the general public. Over 400 people gathered to watch the documentary and participate in a post-screening discussion with a panel of leading scientists, physicians, and health professionals, including Maria Gloria Dominguez-Bello, scientist at New York University, former professor of the University of Puerto Rico in Rio Piedras and also a project director of a worldwide baby microbiome project and one of the participants in the documentary; Ana Parrilla, Professor of Public Health Medical Sciences Campus and public health doctor specialist in human lactation and breastfeeding; Clemente Diaz, pediatrician, clinical researcher and professor at the School of Medicine of the University of Puerto Rico; Karla Leavitt, an obstetrician and perinatal researcher; and Tania Jesus, certified lactation educator and a community doula and co-creator of the local health campaign inne-CESAREA.org.

The star panel, moderated by Godoy-Vitorino, discussed new obstetric practices that can minimize impact on the microbiome of newborns, and also discussed how breastfeeding, diet, and maintaining a healthy microbiome are important to improving quality of life. The panel answered questions from the audience for over three hours, resulting in a fruitful exchange of ideas and the establishment of new synergies between academia, professional groups and health organizations, all committed to promoting new education strategies in Puerto Rico that will serve to offer the best and most beneficial health practices to the community.

Students were thrilled that they were able to host such a high-magnitude event that had great student and community participation, significant social media coverage, and most importantly, provided a direct benefit to the local community. The success of this program is a testament to the hard work of
the students, and clearly demonstrates the impact that dedicated students, their mentors and other volunteers can have in providing valuable programming and education opportunities in their local communities.

For more information about local ASM Branches and Student/Postdoc Chapters, visit www.asm.org/branches.

Arnold Rodriguez
President IAUPR-MC Student Chapter

Filipa Godoy-Vitorino
IAUPR-MC Student Chapter Mentor

Student News from SCASM 78th Annual Meeting

The Southern California Branch of ASM (SCASM) hosted a student science day on Saturday, 25 October 2014 at its 78th annual meeting held at the Hyatt Regency Hotel in La Jolla, Calif. Twenty-four students from universities in southern California participated in the collegiate poster session where judges reviewed their posters and asked the presenters questions about their work. Winners of the competition were awarded a travel grant to attend the National 2015 ASM Meeting in New Orleans, La. Travel grants were funded by bioMerieux, Inc. and by SCASM.

Winners of the SCASM 78th Annual Meeting Collegiate Poster Session were Bryan Hancock of the University of California San Diego (PI, Kelly Doran), Ph.D. level award for his poster “Regulation of Tight Junction Complexes in the Brain Endothelium by Meningeal Pathogens;” Alicia Davis of Cal State San Bernardino (PI, Laura Newcomb), Master’s level award for her poster “Characterization of Influenza Nucleoprotein Body Domain as Antiviral Target;” and Jordan Todd of the University of California San Diego (PI, Victor Nizet), Undergraduate level award for his poster “Group A Streptococcus Survival in Macrophages Results in Cell Death and Inflammation.”

Other meeting activities included a career session where the students spent time with representatives from industry, public health, clinical microbiology, and research to learn about “a day in the life of” by using a “speed dating” format. Students also visited the vendor booths to learn about various products and their impact on the field of Microbiology.

SCASM is pleased to continue the tradition of providing a forum to support student research and to educate students about various career opportunities within the field of Microbiology. Discussion is underway on plans to expand the scope of the program at next year’s meeting and provide a forum for teacher in-service education.

To learn more about SCASM programs, please visit the Branch website at http://www.scasm.org/. For general information on ASM Branches, visit www.asm.org/branches.

Ann Grasmick
SCASM Student Session Coordinator

(l-r) Denise Deines, Regional Business Manager, bioMerieux, Inc.; Jordan Todd, UCSD; Alicia Davis, Cal State San Bernadino; Bryan Hancock, UCSD; Elizabeth Marlowe, SCASM President; and Ann Grasmick, SCASM Student Session Coordinator.
Like 80% of other women in STEM disciplines, I am married to another Ph.D. We are both biologists and often collaborate together, but have very different research programs. He’s now tenured, and I am a postdoc. We would like to move closer to family, so I am applying for academic jobs and have had several on-campus interviews. When would you recommend bringing up the spousal hire situation? For each interview, I’ve done this at different times depending on the feel and size of the institution and/or when the illegal questions are asked. I’ve heard many different philosophies on this and still cannot make a decision as to which is the best way to proceed, assuming I get another interview.

When should an applicant divulge their marital status? We all know it is illegal to inquire about marital status, however some entities ignore the rule, or more commonly an interviewer inadvertently introduces the topic. Can there be advantages to discussing marital status and issues of a trailing spouse in advance?

The Microbe Mentor reached out to several colleagues to gather their responses about how to handle this situation so many of us have faced. Beth Lazazzera, an Associate Professor at University of California–Los Angeles, comments “I think the best time to tell an institution about your spouse who will also need a new job is once you have an offer. It is very natural for the issue of being married to come up during informal discussions.”

There may be an advantage to broaching the topic of a trailing spouse, as it may give the hiring institution more time to come up with a position for the spouse. Lazazzera continues, “However, too early on in the interview process, and the possibility of having to find a position for a spouse can inadvertently cause your application to be looked at less favorably. Thus, I would argue that it is best to bring this up after the offer is made.”

Amy Cheng Vollmer, Professor and Chair of Biology at Swarthmore College, concurs and advises “to have nothing about the spouse [mentioned] in any documents: cover letter, recommendation letters, etc. Let the candidate’s own merits alone get her the interview. In most cases, I would not even mention it during the interview; instead nail the job lecture/talk!”

Vollmer further notes that you should consider the employer’s hiring atmosphere in general. “Spousal hire is always tricky, especially at small schools where faculty positions cannot be generated quickly. But even small schools in and near metro areas are in contact with other institutions. Assistance with spousal employment is definitely possible.”

In the event that marital status is brought up during the interview—even though it should be off-limits—Vollmer comments that “instead of volunteering information, the candidate should ask how the institution assisted spousal employment cases in their previous three or four hires. Not only in that department, but at the institution. That gives the candidate a great deal of information—she should not volunteer much about her spouse, unless the chair of the search committee is sounding very positive.”

As someone who has worked to recruit faculty members, Victor DiRita of Michigan State University thinks that having that information when candidates are coming for a second visit, even before an offer is made, works in their best interest. “That way, we can identify potential employment arrangements for the spouse prior to his or her joining in on the second visit—which is typical—and their day(s) during the visit can be spent talking to the right people and sharing their CV or resume around. Waiting until an offer is actually on the table means we’ve lost a lot of time that could have been spent working on something for the spouse. In recruiting a candidate, I think the second visit is really a chance for us to recruit the spouse; the more we do on that front ahead of the visit, the better off both we and the candidate will be.”

Ultimately, any hire should reflect the job seeker and their skills, not their marital status. How to deal with a trailing spouse is a common issue in faculty hires, and so departments are prepared for these scenarios. There may be a handful of situations however, where revealing information about one’s partner may actually yield a benefit. Wade E. Bell, Director, Virginia
Military Institute Research Labs, has hired faculty at multiple institutions over the past 20 years, and offers this perspective: “I have seen in several cases a search committee swayed by a candidate who has revealed that their partner is already a good fit for the community and will not need any special consideration. This behavior can be accentuated following a failed search that had trailing partner issues as a component of the recruitment failure. We all want to hire the best candidate, however many searches yield several highly desirable choices. It is not inappropriate for a candidate to use any appealing aspect of their overall fit for a job given the increasingly competitive market.”

Beth Lazazzera
Beth Lazazzera has been a professor at UCLA for 15 years, where she runs a research lab and mentored undergraduate researchers, graduate students, and postdocs. She has also taught classes to undergraduates about Microbiology and to graduate students about Genetics.

Amy Cheng Vollmer
Amy Cheng Vollmer has been teaching in a small liberal arts setting since 1985. She encourages the practice of networking and mentoring for professionals at all levels of training. She believes that establishing a healthy work-family balance should be a high priority.

Wade E. Bell, Ph.D.
Wade E. Bell, Ph.D., is a Professor of Biology at the Virginia Military Institute and Director of VMI Research Labs. His specialty is eukaryotic microbiology. In addition to serving as Chair of ASM’s Student Membership Committee, he also represents the Virginia Branch as Councilor at ASM’s Council Policy Committee.

Victor J. DiRita
Victor J. DiRita is a Professor of Microbiology and Immunology and Associate Dean for Graduate & Postdoctoral Studies at University of Michigan Medical School, and Chair of the ASM Membership Board. He studies biology and pathogenicity of the human intestinal pathogens Vibrio cholerae and Campylobacter jejuni. He has worked closely with faculty, trainees, and professional development staff to encourage and support career preparation activities by pre- and postdoctoral trainees. In June 2015 he will join the Department of Microbiology and Molecular Genetics at Michigan State University as Rudolph Hugh Professor and Chair.
Reviews and Resources

BOOK

Justice for Malcolm: Human Sacrifice under U.S. Bioterrorism

This is an important book that is well worth reading. It concerns the death of University of Chicago Associate Professor Malcolm Casadaban from laboratory-acquired *Yersinia pestis* (the bacteria that causes plague) and therefore for most of us also questions of how university laboratories do research with dangerous pathogens—how we should and should not. However, the title is misleading as there is no justice: Malcolm died painfully, with nobody aware of what had happened until days later. It was not human sacrifice, but possibly was just an unpredicted accident, although author Chou makes the case that Malcolm’s death resulted from the use of an attenuated laboratory strain as a live vaccine. This reader finds the evidence she presents on this possible but unconvinced. The laboratory in which Malcolm worked and was infected was not directly involved in offensive bioterrorism, but rather trying to understand the basic molecular biology of pathogenesis of *Yersinia* with a goal of developing useful vaccine proteins or strains. That does not sound evil or inherently dangerous.

This reviewer, who knew Malcolm for most of his scientific life, and who spent a couple of hours with Malcolm in the *Yersinia* lab a few months before his death (sitting by the bench in the lab discussing and planning future experiments) does agree with author Joany Chou about two or three key conclusions of the book. Neither Malcolm nor the head of the *Yersinia* group at the University of Chicago even thought of *Yersinia* as the cause of his weeklong, flulike illness that had days earlier taken him away from lab work and into the University health clinic. They both should have; and if either had, then antibiotic treatment would have readily cured him. This is impossible to understand. After Malcolm died, the university pulled together in an ugly manner to cover up (as Joany Chou and I agree) what had happened and to blame the victim, putting out statements that Malcolm was responsible by sloppy, dangerous behavior. This was not true and is unfair. Casadaban was sometimes relaxed and but often excessively stringent, as are others with knowledge and understanding. In a university chapel memorial three days after his death, the head of the *Yersinia* research group that included Casadaban held Malcolm’s lab notebook in his hand while praising him—but then strangely (to me, sitting there) said nothing about the manner of death. The strong actions to protect the university by clear cover-up are basically as author Chou describes.

Although over $600,000 were spent soon after Malcolm’s death in cleaning up facilities and replacing supplies and equipment, the university lab stayed sloppy enough (if you want to call it that) that they had a second frightening infection two years later: a researcher in the same laboratory room came down with laboratory-acquired anthrax-like disease (see *Science* magazine, 12 September 2011, http://news.sciencemag.org/2011/09/updated-university-chicago-microbiologist-infected-possible-lab-accident), but the researcher responded to appropriate antibiotics and surgery and survived. The university then (after sequencing the bacterial genome, as happened also to Malcolm’s *Yersinia*) decided that it looked like *Bacillus anthracis*, that it caused the disease like anthrax, but it really was a slightly different anthrax-causing bacterium. Now, microbiologists know that *Yersinia* and *B. anthracis* are quite different bacteria, with the major common factor that they kill humans rapidly and with high probability. Again blame and the mode of infection (skin, as was possible with Malcolm, although Joany argues that he ingested the *Yersinia*) were raised after this second, highly improbable, but maybe avoidable situation working in the same room on these dangerous bioterrorism bacteria.

Further work was immediately moved from the University of Chicago campus to a newly opened (just after Malcolm’s death) high-security facility at the Argonne National Laboratory grounds some 27 miles away. It took a second experience, and not just Malcolm’s death, to learn that lesson. But perhaps Malcolm’s death helped save the life of this second person, as it was recognition of the problem and then the rapid implementation of intensive diagnosis and treatment that occurred. All work on the anthrax-related bacterial strain in the open lab quickly stopped and was transferred to the Argonne facility.

There is another worrisome aspect of Malcolm’s death from septicemic *Yersinia* infection; that is, how did the laboratory bacteria get into his
body? Unlike historic bubonic plague (of the lymph nodes) that is transmitted by flea bites, and pneumonic plague (transmitted by breathing in airborne bacteria), the alternative possibilities here were through a small cut in his skin or by oral ingestion. The autopsy evidence was apparently unclear, but the University of Chicago (and U.S. federal government supporting the university) sought to protect itself from responsibility by blaming Malcolm, claiming that he was sloppy about lab coats and rubber gloves. Joany Chou argues that oral ingestion of a large number of bacteria as a live vaccine was the mode of infection, based on published protocols from the same laboratory, planning tests by ingestion of a different Yersinia species. There was a protocol for mice and another for ingestion by eight human volunteers, including Casadaban. This reader cannot see any way to know whether that protocol was ever put in to use. The absence of evidence is not evidence.

In summary, this is an extraordinary book seeking justice for a former spouse who clearly died needlessly from a laboratory-acquired infection that could have been readily treated if Malcolm or the laboratory head had recognized what was happening over the several days in which they had the opportunity. They did not. Although full of accusation which this reader finds less than compelling, it is solid, with a large number of official government reports and forms covering many aspects of what happened. It has serious lessons for all concerned with public health and university research. For those reasons alone, it deserves a wide readership.

Simon Silver
University of Chicago
Chicago, Ill.
Application Deadlines

American Board of Medical Laboratory Immunology (ABMLI) Certification. Certifies the expertise of doctoral-level scientists seeking to direct laboratories engaged in the immunological diagnosis of human disease. ABMLI certification is the highest credential available to practicing medical laboratory immunologists and is recognized under CLIA '88 as one of the acceptable personnel requirements for high complexity laboratory directors. ABMLI certification is achieved by passing an online multiple-choice exam that is offered daily in the month of August at over 700 testing centers worldwide.

WWW: http://www.asm.org/abmli

Deadline: 1 June 2015.

ASM-LINK Undergraduate Faculty Research Initiative (UFRI) Fellowship. Early-career (and future) undergraduate STEM educators are encouraged to apply for a 2015 ASM-LINK Undergraduate Faculty Research Initiative (UFRI) Fellowship. This new professional development resource trains STEM faculty to develop undergraduate research programs by initiating successful research partnerships. As part of the fellowship, ASM LINK will provide travel subsidies of up to $2,000 to (i) increase participation of undergraduate STEM educators at seven eligible ASM-sponsored research conferences, (ii) encourage networking and collaborations with potential research partners, and (iii) access resources and mentoring to advance undergraduate research programs. Fellowship applications are accepted on a rolling basis for each of the seven eligible ASM conferences. Deadlines are 13 and 27 July to be considered for UFRI Fellowships to two ASM topical meetings focused on Pseudomonas or Rapid Next-Generation Sequencing.


ASM Meetings Calendar

12–16 June 2015.
Prokaryotic Cell Biology and Development.
WWW, http://conferences.asm.org/

8–12 September 2015.
ASM Conference on Pseudomonas 2015.
Washington, D.C.
WWW, http://conferences.asm.org/

17–21 September 2015.
ICAAC/ICC Meeting.
San Diego, Calif.

1st ASM Conference on Rapid Next-Generation Sequencing and Bioinformatic Pipelines for Enhanced Molecular Epidemiologic Investigation of Pathogens.
Washington, D.C.
WWW, http://conferences.asm.org/

24–29 October 2015.
7th ASM Conference on Biofilms.
Chicago, Ill.
WWW, http://conferences.asm.org/

2–5 November 2015.
Chicago, Ill.
WWW, http://conferences.asm.org/

13–17 April 2016.
13th ASM Conference on Candida and Candidiasis.
Seattle, Wash.
WWW, http://conferences.asm.org/

31 July–3 August 2016.
ASM Conference on Streptococcal Genetics.
Washington, D.C.
WWW, http://conferences.asm.org/

4–7 August 2016.
2nd ASM Conference on Experimental Microbial Evolution.
Washington, D.C.
WWW, http://conferences.asm.org/

9–12 September 2016.
6th ASM Conference on Beneficial Microbes.
Seattle, Wash.
WWW, http://conferences.asm.org/

ASM Conference on Infection and Cancer.
Washington, D.C.
WWW, http://conferences.asm.org/

11–14 December 2016.
ASM Conference on Antibacterial Development.
Washington, D.C.
WWW, http://conferences.asm.org/

About the Calendar

The ASM Meetings Calendar is provided as a service to readers of Microbe. It includes annual meetings and conferences organized by the Society. Detailed information for these events is published in the ASM Meetings and Conferences insert, which appears bimonthly in the center of Microbe.

As an added benefit of membership in ASM, an online calendar of microbiology-related meetings hosted by ASM and by other organizations is available through the ASM website. Any organization may submit items for the online calendar provided that submissions are of obvious interest to microbiologists. ASM will not permit announcements to appear in the calendar when the subject matter and dates conflict with ASM meetings or workshops. The calendar is located at https://info.asm.org/index.php/meeting-and-event-calendar. All entries in the online calendar are limited to conference name, dates, location, website, and contact information (person, address, telephone, fax, and/or e-mail). When websites and e-mail addresses are provided, links to them will be established. Because of the volume of submissions received, ASM staff is unable to provide proofs or other confirmation of receipt of each listing. Submit items for the online calendar through the “Add a new event/deadline” link on the Meeting and Event Calendar page.
Small Things Considered

Chromosome Organization the Pseudomonas Way
by Christoph Weigel

Members of the family Pseudomonadaeae (Gammaproteobacteria) are ubiquitous and make up a respectable percentage of the microbes in any sample from air, water, soil, plant or animal skin, plastic or metal surfaces. They grow aerobically and anaerobically, most are cultivatable, many are halotolerant, and there are psychrophilic as well as thermophilic family members. They “use quorum sensing” and proliferate happily as planktonic cells but are also champions of a life in biofilms, e.g., in the lungs of patients with cystic fibrosis. Pseudomonads have by far the largest genomes among the known Gamma-proteobacteria. For instance, P. aeruginosa PAO1 has a 6.3-Mb circular chromosome that codes for ~5,600 genes.

P. aeruginosa is one of the exceptional cases of bacteria with two functional replication origins (oriCs) for a single replicon, located ~6 kb apart. Both are DnaA dependent, yet only one (oriC1) can independently drive chromosome replication. The role of oriC2 is unknown. In any case, firing of both origins alternately or even simultaneously would hardly cause problems with cell cycle regulation as the distance between them seems negligible compared to the ~3 Mb origin-terminus separation.

We know little about the regulation of initiation of chromosome replication in P. aeruginosa. In Escherichia coli, DiaA promotes higher-order complex formation of the initiator protein DnaA bound to oriC prior to initiation, while Hda—in concert with the β-clamp subunit of the replicative DNA polymerase—inactivates DnaA shortly after initiation by stimulating DnaA’s intrinsic ATPase activity. Genes encoding homologs of E. coli DiaA and Hda are present in the P. aeruginosa genome, but neither protein has been looked at experimentally.

By contrast to E. coli, a functional equivalent of the Dam/SeqA system that limits initiation to a narrow time window has not been found in P. aeruginosa, nor is it known if its dnaA gene is subject to autoregulation. Likewise, the termination step of chromosome replication is only rudimentarily understood here. From the presence of E. coli homologs for XerCD and FtsK, we conclude that FtsK translocates DNA across the septum after XerCD recombinase disentangles the fully replicated chromosomes at the dif site during the final stage of chromosome segregation. Clearly, the regulation of replication in P. aeruginosa demands further studies.

Like most other bacteria, P. aeruginosa compacts its chromosome by negative supercoiling of the DNA through the combined actions of topoisomerases and nucleoid-associated proteins (NAPs). Unlike classical repressors, NAPs don’t usually bind to well-defined binding sites in promoter regions of genes but instead bind to more relaxed recognition sequences and particular DNA structures. When bound to DNA, NAPs induce bends and kinks, and oligomerize to form highly dynamic “bridges” between neighboring ~10-kb topological domains. Both eukaryotes and prokaryotes use a set of SMC (structural maintenance of chromosomes) proteins to “clamp” together those 10-kb domains. SMCs, together with their accessory proteins, are called condensins. P. aeruginosa PAO1 encodes two condensins that are essential for faithful chromosome partitioning during replication, but their mechanisms are not yet fully understood.

Many bacteria, including P. aeruginosa, possess a ParABS system that organizes and compacts the chromosome at a higher level and actively controls the movement of chromosome segments during replication. Present models suggest that ATP-bound ParA oligomerizes into filaments along the cell axis and loosely contacts the DNA. ParB dimers bound strongly to parS sites close to the replication origin stimulate the intrinsic ATPase activity of ParA upon contact with a filament tip, causing ParA to depolymerize. Alternating ParA polymerization-depolymerization pulls the tethered chromosomes along the ParA filament, thus spatially separating them. P. aeruginosa parA or parB mutants show severe growth defects, including aberrant chromosome segregation.

The above may sound like an extended to-do list rather than an established choreography, but recently Vallet-Gely and Boccard gained deeper insight into the ballet of chromosome organization in P. aeruginosa by fluorescently tagging various loci and following their localization over the cell cycle. At various growth rates, they found oriC at mid-cell and ter at the newer pole, resulting in an overall longitudinal orientation of the replicochromes. The story continues to unfold.

Christoph Weigel is lecturer at the Life Science Engineering faculty of HTW, Berlin’s University for Applied Sciences.


Join the American Society for Microbiology (ASM) and the International Society of Chemotherapy (ISC)’s International Congress of Chemotherapy and Infection (ICC) for the joint ICAAC/ICC 2015!

Offering unmatched opportunity for discussion, cross collaboration, and advancement, this joint meeting will bring together a rich history of debating major advances in drug development and infectious disease research with a focus on examining antibiotic resistance, new antibiotic development and antibiotic stewardship. This will be 2015’s principal meeting for clinical microbiologists, infectious disease physicians, researchers, and pharmacists to attend to better improve the diagnosis, prevention, and treatment of infectious diseases around the globe.

Follow all the meeting updates and conversations on Twitter using #ICAAC/ICC

Register today at www.icaac.org/icaac-icc

IMPORTANT DATES:

Abstract submission deadline: May 21, 2015

Discounted registration rate deadline: August 6, 2015
MANUAL OF CLINICAL MICROBIOLOGY

ELEVENTH EDITION

Editors-in-Chief: James H. Jorgensen, Professor Emeritus and Research Professor of Pathology, University of Texas Health Science Center; Michael A. Pfaller, Professor Emeritus, Clinical Microbiology, University of Iowa and Chief Medical Officer, T2 Biosystems

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FRED C. TENOVER,
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Revised by a collaborative, international, interdisciplinary team of editors and authors, this edition includes the latest applications of genomics and proteomics and is filled with current findings regarding infectious agents, leading-edge diagnostic methods, laboratory practices, and safety guidelines. This seminal reference continues to set the standard for state-of-the-science laboratory practice as the most authoritative reference in the field of microbiology.

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