PERSPECTIVES ON RESEARCH INTEGRITY

A collection of essays focusing on the importance of ethics consideration within the scientific community

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Research misconduct and other ethical violations in science continue to be matters of concern to the international research community. Perspectives on Research Integrity addresses the need to provide ethics training early and often—in classroom settings and throughout a researcher’s career.

Written by ethics and education experts, Perspectives on Research Integrity presents an enlivened discussion on the globally important topics of responsible conduct of research and ethics education. It synthesizes the current state of RCR and considers future directives and requirements.

A resource for how to teach RCR, Perspectives on Research Integrity was developed specifically for educators, researchers, and RCR offices to train responsible researchers. It is also useful as ancillary readings for students in any course involving research ethics.


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Shannon Weiman

Amycolatopsis mediterranei, which makes rifamycin B, can be engineered to produce analogs that are active against rifamycin-resistant strains of M. tuberculosis.
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Extracellular Enzymes in Soils

I found the recent article in Microbe (April 2015, p. 178) in the Small Things Considered section (“Microbe, Enzyme or Mineral? a Riddle in the Soil”) interesting and appreciated the focus on extracellular enzymes in soils. However, the presentation leaves the reader with the impression that the paper reviewed (J. Blankinship et al., Soil Biol. Biochem. 71:68–75, 2014), is the only research done on the topic and that this is new research; specifically, “the first study that rigorously attempts. . . .”

I would point out that Douglas McLaren at UC Berkley was the first to fully investigate this topic starting in the 1950s with gamma irradiation (the same method used by Blankinship et al.) and did research on extracellular enzyme stabilization in the soil matrix for more than 15 years. A seminal paper on this was McLaren et al. (1962) that utilized gamma irradiation. There have been others, such as Jeff Ladd and Ralph Foster in Australia, who used fluorescence and microscopy to visualize extracellular enzymes in soils at nanometer scales. John Skuja at Utah State worked through the 1970s and 1980s on extracellular enzymes in soils and published a comprehensive book on this topic in the 1970s. M A Tabatabai was the first to use chloroform fumigation as a sterilizing agent in relation to soil enzymes (the same method used by Blankinship et al.) and spent his whole career working on extracellular enzymes. Tom Speir in New Zealand and later from my lab, we used microwave irradiation to study stabilized enzymes. Besides the numerous research papers, a number of books have chapters that review the research and theory of extracellular enzymes in soils. Some of the key papers and books on this topic are listed below.


Richard P. Dick
Ohio State University, Columbus
Grounds for Suspicion

Eight simple criteria can help us to dismiss dubious claims in science even before we look at the detail

Bernard Dixon

I have never met Jack Harmon of Southwest Research Institute in San Antonio, but I’m grateful to him for sending me, some years ago, a list of rules he compiled as guidelines for being suspicious about alleged breakthroughs in science. Bothered by glamorous claims in medicine and science that turned to naught, he was driven to a peak of irritation by a report of a revolutionary motor engine. “When it gets hot, I can make it go with 90 per cent water and 10 per cent alcohol,” the proud inventor boasted in a press release issued by a major PR company. “Three of my mechanics have a way of making it run on 100 per cent water.” So Harmon prepared his list of reasonable grounds for suspicion about any new discovery or breakthrough. Here they are, with my own comments added:

1. It is a “cure” in its approach and promises an immediate miracle. I came across an example of this only last week on the Web—a dramatic cure for even the most aggressive and intractable cases of candidiasis, based on an extract of grapefruit prepared by a “special, secret process”. Suspiciously, perhaps, it appeared on a site (alongside entirely orthodox ones about candidiasis) claiming that huge numbers of cases go undiagnosed. The main symptoms, it said, were sporadic tiredness and occasional depression.

Another example, easy to dismiss now but which received a vast amount of attention at the time, is the story of William Summerlin, a young skin specialist at the Sloan-Kettering Institute for Cancer Research in New York City. In the early 1970s, he claimed to have overcome the rejection of transplanted foreign tissue by some sophisticated method which nobody had ever dreamed of before. In fact, he had forged his results by marking the skin of white laboratory mice with a black felt-tipped pen. Joseph Hixson tells the story in The Patchwork Mouse (Anchor Press, 1976).

2. It originates with an untrained person in a picturesque and primitive locale. The amateur physicist who works in a caravan parked in Yellowstone National Park and who claims to have discovered a new form of electromagnetic radiation, probably hasn’t—even if the caravan is called the Celestial Harmonics Division of Incorporated Research International. But this rule does worry me a little. Louis Pasteur was not trained to study bacteria. He was a chemist. Likewise, none of the British scientists who made the greatest contributions to operational research during World War 2 was trained in OR; several were biologists.

3. It repeals one or more long established scientific laws. I once attended a lecture at London’s prestigious Royal Institution during which a distinguished professor of electrical engineering demonstrated a machine which, he insisted, violated gravity. He had to modify his view later after intercession by colleagues. Newton’s laws of motion still stand. Perpetual motion devices never work.

And remember “anomalous water”? Felix Franks told this story in Polywater (MIT Press, 1981). Allegedly discovered by Russian scientist Boris Deryagin, but later attracting research funding from the U.S. Navy, polywater promised momentous practical applications but also presaged worrisome dangers. Most fearsome was the possibility that even a tiny quantity of anomalous water, escaping from a laboratory, might polymerize all of the water on the planet, which would become biologically unavailable. As the great J. D. Bernal pointed out in a letter to Nature, if this could happen it would have happened long ago. Polywater was simply dirty water.

4. It is eagerly sought by foreign nationals but is being offered for one last time (as a patriotic duty) to American investors. As a British subject, I should perhaps restrain comment on this one. But I do note that when a UK pioneer claims that
the government or funding authorities are neglecting his unique approach to the problem of, for example, antibiotic resistance, he or she invariably adds a warning: “Remember what happened to penicillin.” This is a reference to the allegation, not wholly true, that the UK Medical Research Council failed to patent penicillin, discovered in London and developed in Oxford, and thereafter had to pay royalties for ever more to U.S. and other overseas companies.

5. **It is being held back by a conspiracy.** I have met several scientists over the years who assured me that their great work was being suppressed by a conspiracy. This usually involved a national academy of science, sometimes *Nature* or *Science*, and/or a television or radio company. (I cannot name names because such people are usually highly litigious, even with folk who try to help them.)

6. **Claims are made of presentations at scientific meetings but no research paper is available.** Not quite accurate. Crusading cranks, for example, are accomplished at writing research papers, which they will be able to present to some audience somewhere. Often they have them expensively printed or, nowadays, displayed on an impressive website. Sometimes, the “findings” prove to be “internal” disclosures read only by the scientist’s family or reprints from obscure journals run by homoeopathic charities). Beware too of the inventor who brandishes a patent specification in front of you. The barmiest idea can be patented, as long as no one has patented it previously.

7. **There is no prototype working model.** Although not generally relevant to microbiology, there is a strong parallel in the field of bioremediation. Time and time again, I have received emails sent by people who have isolated from the soil or sea (often in an exotic location—see 2 above) a hitherto unknown organism capable of detoxifying former industrial sites or rendering safe the most powerful and recalcitrant poisons. The researcher has achieved these wonders in a test tube or on a Petri dish. But he or she has not demonstrated the feasibility of an actual working process on even a modest scale, nor of course established that it might be economically feasible.

8. **Certain parts of the scheme or apparatus must remain secret.** Entirely dependable. Secret parts have been the undoing of many exponents of perpetual motion over the years. I was fobbed off with the secret part gambit when investigating the case of a British biomedical charlatan who invented and publicized a “black box” many years ago. I was shown the box, which he was using to treat everything from arthritis to coronary disease, the key component of which had to remain partly hidden despite the man’s insistence on openness with the press (this could have been because, as he told me, his device was also being held back by a conspiracy).

In all, then, Jack Harmon’s principles are jolly useful, not infallible but strongly indicative. Others could be added. Not infrequently, charlatans and the misguided super-salesmen of science either talk incessantly, smell mouldy, or wear colorful bow ties—but again, none of these signs is totally trustworthy. Results too good to be true should ring alarm bells (though this could mean disqualifying all-time greats like Gregor Mendel, whose pea breeding ratios were simply too good to be true). The one absolutely diagnostic situation is any approach from an enthusiast with a file, whether printed or in the computer, consisting of letters (usually an indiscriminate mixture of rejections and polite acknowledgments) from other people he has approached with his brilliant notion. If that ever happens to you, don’t have anything to do with him.

Don’t even e-mail him or write him a letter. He will probably forward a copy to me.
**Current Topics**

**RESEARCH ADVANCES**

**Undersea “Autoendoliths” Take Sulfate and Methane, To Make Rocks from CO₂**

Carol Potera

Recently uncovered microbes that live beneath and along the seafloor consume methane and sulfate ions, while generating bicarbonate that they use to build limestone rocks and then entomb themselves in those pores and crevices, according to geobiologists Victoria Orphan and Jeffrey Marlow at the California Institute of Technology (Caltech) in Pasadena and their collaborators. They propose calling the members of these microbial consortia “autoendoliths” to distinguish them from other rock-dwelling microbes, called endoliths, that either degrade rock or passively abide in rocky cavities. Details appeared in the July 2015 *Geobiology* (doi:10.1111/gbi.12131).

The autoendoliths and their limestone structures are found in several sites along the West Coast of North and Central America, including Hydrate Ridge near the Oregon coast, Eel River basin off the coast of northwestern California, and near methane seeps off the coast of Costa Rica. The Caltech researchers and their collaborators collected samples using *Alvin*, a submersible vessel.

By consuming methane, these mixed archaeal and bacterial communities likely prevent methane from entering the water column and escaping into the atmosphere, according to Marlow. Methane is much more potent greenhouse gas than carbon dioxide, and “tracing its flow through the environment is important for understanding carbon cycling and climate models,” he says. The autoendoliths are “a reminder that the biosphere and geosphere are intimately linked and interact with each other. There’s a dynamic relationship between rocks and microbes that’s larger and more complex than we ever thought.”

These recent findings by Marlow and coworkers “make us think differently about endoliths and methane-driven carbonate structures,” says Kenneth Nealson at the University of Southern California in Los Angeles. “They make a good case about the need for a term for rock-forming endoliths that are metabolically involved with their substrate.” However, whether these microbes warrant their own specially named category remains an open question—one not yet etched in stone, he suggests.

Carol Potera is a freelance science writer in Great Falls, Mont.

*Rockfish among deep-sea carbonate (limestone) formations at Hydrate Ridge off the Oregon coast.* Such formations are built by microbes that consume methane and sulfate ions and produce bicarbonate, forming structures that can rise hundreds of feet from the sea floor. (Photo credit: L. Levin.)
RESEARCH ADVANCES

Modelers Beware: Phytoplankton Adapt Quickly to Climate Change

Barry E. DiGregorio

Despite widely held views suggesting that phytoplankton could take a century to adapt to climate change, direct measurements indicate that they are perhaps 10 times faster when reacting to changes in sea temperatures and incident light, according to Andrew Irwin of Mount Allison University in Sackville, New Brunswick, Canada, and his collaborators there and in the United States and Venezuela. Thus, they note, climate change modelers should consider revising their projections because such biological communities likely could respond to what happens around them far faster than anticipated. Details appeared 5 May 2015 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1414752112).

“I’m not sure if the temperature adaptation was particularly unexpected,” Irwin says. “But many researchers have been acting as though phytoplankton won’t adapt quickly—over a few years to a decade—to changes in temperature.”

“However, it seems likely that climate change will affect many phytoplankton species in two ways,” he continues. “First, the environments in which each species is found may change. Second, large-scale changes in temperature, ocean circulation, and the distribution of resources necessary for phytoplankton to grow will alter the rates and distribution of primary production.” Thus, he and his collaborators conclude, “Community ecosystem models can no longer assume that phytoplankton cannot adapt.”

“The authors are, to my knowledge, the first to present evidence for decadal-scale evolutionary adaptation of phytoplankton in a natural marine community,” says S. Lan Smith of the Japan Agency for Marine-Earth Science and Technology in Yokohama. “However, given the genetic variability within species and the constant transport of plankton in the ocean, the local changes they infer in niches could also have resulted from immigration of phytoplankton... Nevertheless, given the great numbers and short generation times of phytoplankton, and independent evidence of rapid adaptation from laboratory experiments, I agree with the authors [about] modeling studies.”

“The results of this work will come as no surprise to many biologists; organisms adapt over time to counter changes in their environment,” says Kevin White of Swansea University in Wales, United Kingdom. “However, critically, this paper may jolt many ecosystem modelers to reappraise their models. [Irwin’s] results hopefully will catalyze [that] much-needed review.”

“I do not think anyone in the community that works on phytoplankton physiology would have been at all surprised by these results,” adds Jack A. Gilbert from Argonne National Laboratory, affiliated with the University of Chicago in Illinois. “This is an interesting longitudinal time series, [but] the impact of these findings will be extremely minimal, which [Irwin and his collaborators] fully admit.”

Barry E. DiGregorio is a freelance writer in Middleport, N.Y.

MINITOPIC

Microbiology Policy Bulletin Board

Recent national and international developments involving microbiology and related science policy matters include:

- Reflecting a continuing concern over antibiotic resistance issues, the Obama administration in June invited representatives from more than 150 food companies, retailers, and human and animal health stakeholders to a “White House Forum on Antibiotic Stewardship.” The President also signed a memorandum directing federal departments and agencies to create “a preference for meat and poultry produced according to responsible antibiotic use.”
- In a related development, officials of the Food and Drug Administration plan to expand data collection on the use of antibiotics in agriculture.
- Further, the National Institutes of Health and the Biomedical Advanced Research and Development Authority in June announced a competition in which up to $20 million could be made available for the delivery of one or more successful rapid point-of-care diagnostics that may be used by health care providers to identify bacterial infections.
- The World Health Assembly (WHA) in May adopted a global action plan on antimicrobial resistance, urging member states to implement compatible national action plans within two years.
- WHA also called on member nations to allocate adequate resources for introducing vaccines and developing immunization programs.
- Back at the national level, several members of the House of Representatives Energy and Commerce Committee are continuing to question Centers for Disease Control and Prevention Director Tom Frieden and Secretary of Defense Ashton Carter about incidents in which samples containing “live anthrax” were mistakenly shipped “to nearly twice as many states and three times as many countries as originally reported, [including] 51 labs in 17 states and 3 foreign countries,” the committee members note.

[Random directing federal departments and agencies to create “a preference for meat and poultry produced according to responsible antibiotic use.”]
MINITOPIC
Schooner Tara Plies Oceans, Accruing Microbial Insights

Following three and a half years of plying the oceans and collecting samples from them of phytoplankton and other microbial specimens for analysis, the Tara Oceans consortium began releasing some of its findings this past May. The expedition yielded more than 35,000 planktonic samples from 210 stations in all the major oceans, the investigators report. A partial metagenomic analysis, for example, led to development of a reference gene catalog containing more than 40 million nonredundant, mostly novel sequences from viruses, prokaryotes, and picoeukaryotes, according to Shinichi Sunagawa of the European Molecular Biology Laboratory in Heidelberg, Germany, and several dozen collaborators. Another set of analyses helped to develop a catalog describing about 150,000 genetic types of eukaryotes, many more than described in the published literature, according to Colomban de Vargas of CNRS in Roscoff, France, and collaborators. Details of these and other studies from the Tara voyages appeared 22 May 2015 in Science (doi:10.1126/science.1261359).

ASM MEETING
Multifactorial Resurgence of Pertussis Is, in Part, Vaccine Driven

Jeffrey L. Fox

Pertussis is regaining momentum, even within populations in which vaccines are widely used. That resurgence is “real and multifactorial” and, at least in part, is “vaccine-driven,” says Maria Tondella of the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. She spoke during the symposium “Antigenic Variation, Vaccine-Driven Evolution” at the 2015 ASM General Meeting in New Orleans last June.

By the late 1940s, the first of several vaccines to protect against pertussis came into wide use. In this case, the vaccine derived from whole cells of Bordetella pertussis, the bacterial pathogen responsible for this disease, also known as whooping cough because of the characteristic and often long-lasting coughing spasms that afflict infected individuals. Although highly effective, the whole-cell (WC) vaccine tends to cause side effects, and its use was phased out in the United States (and a bit later in other countries) after 1991 whenacellular, or component-antigen, pertussis vaccines became available.

Not long thereafter, public health officials began to see a rise in incidence of pertussis, according to Tondella. That rise was subtle at first, and nowhere near what occurred before pertussis vaccines were available. Some of the rise can be attributed to surveillance bias and improved diagnostic procedures, and other portions to outright refusal by parents in some segments of the population to allow their children to be vaccinated. California, for example, is “experiencing a pertussis epidemic” that is driven largely by such refusals, according to public health officials at CDC and in California. Another factor is “waning immunity” among those who receive the acellular vaccine, which depends on repeated boosting to remain effective—and, even then, affords less than full coverage but at least protects against the most severe forms of this disease.

During this same period, pertactin-deficient strains of B. pertussis began to emerge, according to Tondella. The adhesin molecule pertactin is considered one of several major virulence factors. Several different types of mutation give rise to these strains, and their prevalences vary geographically, she says. “Vaccinated patients had higher odds of having pertactin-deficient mutants, [which was] the first evidence of a selective advantage.”

CDC and other investigators, who are analyzing the genomes from several hundred isolates obtained from pertussis patients in California and other states during recent outbreaks, find rearrangements among other changes, she adds. “We don’t know what this means in terms of phenotype. But we will need to take these molecular and genomic changes into account to develop better vaccines.”

“The whole-cell pertussis vaccine is still used in much of the world,” says Jason Warfel of the Food and Drug Administration (FDA) in Silver Spring, Md., who spoke during the same symposium. Although “all the vaccines are equivalent in terms of preventing severe pertussis,” he adds, WC vaccines apparently “do a better job at preventing nasopharyngeal colonization and clearing the disease faster than the acellular vaccines. We need to identify the breadth of essential antigens playing important roles in the WC vaccines.” However, because the newer, acellular vaccines are thought to cause fewer side effects than the WC vaccines, the United States is unlikely to go back to using them, he points out.

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

NEW IN ASM JOURNALS
In Leaving Africa Centuries ago, Green Monkeys Lost Viruses

David C. Holzman

After African green monkeys (AGMs) were shipped to the Caribbean during the 17th century—a species introduction that stemmed from the slave trade—two of three blood-borne viruses that these animals carried were lost from this transplanted primate population, according to Eric Delwart of the Blood Systems Research Institute in San Francisco and his collaborators.

viruses
The reduced virome is thought to be due to that early bottleneck in the host population. Details appeared 27 May 2015 in the *Journal of Virology* (doi:10.1128/JVI.00671-15), along with a commentary by Cristian Apetrei and several collaborators from the University of Pittsburgh (doi:10.1128/JVI.00802-15).

The green monkeys that went to the Caribbean, perhaps as pets of the slaves onboard those same ships, lacked two of three blood-borne viruses carried by their ancestors in Africa, according to Delwart. Their absence was due either to chance, if only small numbers of uninfected monkeys made the voyage, or because the hosts consisted only of infants and juveniles that had not acquired the two sexually transmitted viruses, he says.

Although AGMs are found throughout much of Africa, genetic analysis of the Caribbean AGM population suggests they came from West Africa, according to Delwart. Thus, he and his collaborators compared viromes from Gambian to those from Caribbean AGMs. Gambian AGMs harbor simian immunodeficiency virus (SIV), pegivirus, and numerous anelloviruses. However, only the anelloviruses, which were detected in 100% of their Gambian hosts, were also found in the Caribbean. Further, of those three types of virus, only anelloviruses spread among infants and juveniles. Although present in 42% of Gambian AGMs, SIV apparently infects only adults, while simian pegiviruses were found in a mere 7% of Gambian AGMs.

“I was intrigued by the many stories of the extremely high susceptibility of isolated [monkey] populations to epidemic viruses such as smallpox and measles,” Delwart says. “I was also curious as to what the viral burden might be in isolated populations unable to sustain crowd infections. The classic explanation is that they lack pre-existing immunity found in larger populations due to endemic circulation of these viruses.”

These findings underscore the need to protect small, isolated human populations from viral diseases, to which they would lack immunity, says Delwart. “Close contact with anthropologists may bring them in contact with crowd diseases. Making sure that people who approach these populations are themselves completely healthy, fully vaccinated, and carefully dispose of their feces should help.”

The research “provides a compelling proof of concept that human pathogens can be eradicated through host population bottlenecks,” note Apetrei and his collaborators in their commentary.

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**MINITOPIC**

**Circadian Clocks: Stopped in Macrophage; Moved between Bacteria**

When macrophage cells are exposed to bacterial pathogens, a microRNA molecule called miR155 destroys a key protein called BMAL-1 that runs the biological clock within these host cells—stopping it and triggering them to make inflammatory proteins that stimulate further immune responses, according to Garret FitzGerald of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, Annie Curtis of Trinity College in Dublin, Ireland, and their collaborators. Details appeared 9 June 2015 in *Proceedings of the National Academy of Sciences* (doi:10.1073/pnas.1501327112). Separately, the circadian apparatus that operates in cyanobacteria was transplanted into—and then operates within—cells of *Escherichia coli*, according to Pamela Silver of Harvard Medical School in Boston and her collaborators. “This finding goes beyond the transplantability of a circadian rhythm to open new doors to understanding how other modular biological circuits could be transplanted from one species to another,” she says. Details appeared 1 June 2015 in *Science Advances* (doi:10.1126/sciadv.1500358).

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![African green monkeys that were shipped to the Caribbean in the 17th century have limited viromes compared to populations in Africa, leaving them more vulnerable to a number of viruses. (Photo credit: Atamari.)](image-url)

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MINITOPIQUE

Blood Droplet Analysis Yields Snapshots of Viral Exposure History

By scanning peptide epitopes, a new analytic approach called VirScan provides a comprehensive analysis of antiviral antibodies in human sera—effectively, snapshots of an individual’s past exposure to infectious viruses, according to Stephen Elledge Howard Hughes Medical Institute at Brigham and Women’s Hospital in Boston, Mass., and his collaborators. The system, which screens blood samples for any of the 206 species of viruses known to infect humans, uses DNA microarray synthesis and bacteriophage display “to create a uniform, synthetic representation of peptide epitopes comprising the human virome,” they report. “We were in the sensitivity range of 95–100%, and the specificity was good—we didn’t falsely identify people who were negative,” Elledge says. “Instead of testing for one individual virus at a time, which is labor intensive, we can assay all of these at once.” Although an analysis of, say, 100 samples now takes several days to complete, further development is expected to accelerate this analytic process, he adds. Details appeared 5 June 2015 in Science (doi:10.1126/science.aaa0698).

For virologists and other researchers, there is another practical reason to be thankful for the long-term effects of that 17th-century bottleneck, according to Apetrei and his collaborators. Because it proves difficult to export nonhuman primates from Africa, Caribbean AGMs are used more widely for AIDS research. “The existence of a population of AGMs that are free of SIV is critical for AIDS research studies aimed at studying the pathogenesis of SIV infection in natural hosts,” they explain. “All other models used for studying natural SIV infection are endangered.”

RESEARCH ADVANCES

Genes of Deep-Sea Archaea Suggest Two-Instead of Three-Domain Tree of Life

Marcia Stone

A deep-sea archaeon, named Lokiarchaeum for the underwater volcano between Greenland and Norway near where it was found, might be related to the last common ancestor of eukaryotes, according to Thijs Ettema of Uppsala University in Sweden and his collaborators. “The shape-shifting deity ‘Loki’ is described as complex and confusing; thus, ‘Lokiarchaeum’ seems a very appropriate name for our typical prokaryote with a whole bunch of eu-karyotic genes,” he says. “Importantly, the genes we found in Lokiarchaeum could have provided the archaeal ancestor of eukaryotes with a ‘starter kit’ for the cellular complexity typical in the eukaryotes we see today.” Details appeared 6 May 2015 in Nature (doi:10.1038/nature14447).

For example, this Lokiarchaeota encodes actin, the protein that enables present-day amoebas to hunt, catch, and eat their prey. Ettema says he “would never dare to claim that Loki is phagocytic.” What he and his collaborators do claim is that actin-encoding genes and others usually associated with eukaryotes that are found in Lokiarchaeota, including those enabling membrane remodeling and vesicular trafficking, indicate that the onset of “cellular complexity was already underway before the acquisition of a mitochondrial endosymbiont.”

Their findings also favor a two-domain Tree of Life, in which eukaryotes are placed together with a diverse group of archaea known as the “TACK” superphylum because it includes Thaumarchaeota, Aigarchaeota, Crenarchaeota, and Korarchaeota, which share several signature proteins with eukaryotes. Indeed, the Lokiarchaeota-Eukarya affiliation is strongly supported by phylogenetic inferences, according to Uppsala team member Lionel Guy, who supervised the phylogenetic studies. “Our results place Lokiarchaeota in a deeply rooting clade of TACK most closely related to eukaryotes,” he says.

“What’s particularly convincing about the Lokiarchaeota work is the combination of phylogenetics and signature eukaryotic gene content,” says Tom Williams from Newcastle University in the United Kingdom. “The discovery of Lokiarchaeum ful-

MINITOPIQUE

Recalcitrant Lyme May Be Due to B. burgdorferi Forming Persister Cells

Borrelia burgdorferi, the bacteria that cause Lyme disease, can form persister cells, which likely accounts for its recalcitrance to antibiotics during chronic infections, according to Kim Lewis of Northeastern University in Boston, Mass., and his collaborators. Pulsed dosing of drugs, an approach that allows dormant persister cells to become active while antibiotic use is suspended, proves effective against this pathogen in vitro, he says. “The trick to doing this is to allow the dormant cells to wake up ... In principle, a similar regimen [could be developed] for treating patients for this and other chronic diseases.” Lyme disease, which is transmitted via black-legged ticks, affects about 300,000 people each year in the United States, according to the Centers for Disease Control and Prevention (CDC). Details describing the B. burgdorferi experiments appeared 26 May 2015 in Antimicrobial Agents and Chemotherapy (doi:10.1128/AAC.00864–15).
fills a key prediction of the two-domain hypothesis and points the way to further understanding of the prokaryote-to-eukaryote transition,” adds T. Martin Embley, also at Newcastle University.

Not everyone agrees with that analysis. For example, Norm Pace from the University of Colorado in Boulder defends the three-domain tree. “My colleagues and I have studied the deepest [microbial] branches using the most conserved genes—those encoding the ribosomal RNAs (rRNAs)—and conclude, as Carl Woese originally proposed, that the eukaryotic (nuclear) line of descent is primordial, not a derivative of another domain,” he says. “Indeed, the three-domain tree clearly separates the eukaryotic and archaeal lines prior to the radiation of archaea.”

These new findings “unequivocally support the two-domain tree, including [our] recent analyses of rRNA,” Ettema responds.

Whether the Tree of Life consists of two or three domains (or proves not to be a tree, see p. 319), Woese’s “legacy is far more than a three-domain tree,” adds Simonetta Gribaldo at the Institut Pasteur in Paris, France. “He showed the unity of life, discovered the Archaea, revolutionized evolutionary microbiology, and opened up research on deep evolution. If not for Woese, there would not even be a debate.”

Marcia Stone is a science journalist based in New York City.

NEW IN ASM JOURNALS

Prebiotic Boosts Broiler Chicken Feed Conversion

In broiler chickens, feed additives, including prebiotics, are widely used to improve gut health and food conversion. Now Celine De Maesschalck of Ghent University, Belgium, et al. show that xylo-oligosaccharides (XOS) increase meat production per calorie, and improve intestinal morphology, including length of villi. XOS also boosts lactobacilli in the colon and the butyrate-producing Clostridium cluster XIVa in the caeca. The stimulation of butyrate-producing bacteria through cross-feeding of lactate and subsequent effects of butyrate on GI function explains the beneficial effects of XOS on broiler performance, says De Maesschalck. “Our work shows that XOS fulfills two of the three criteria for prebiotic: it is fermented by intestinal microbiota and it selectively stimulates growth of the intestinal bacteria that contribute to host health.”


NEW IN ASM JOURNALS

P450 Enzymes Can Interfere with Antifungal; PPIs Dampen This Effect

Cytochrome P450 enzymes metabolize the antifungal, voriconazole. Some people have P450 enzymes that metabolize voriconazole too quickly, interfering with its efficacy. Certain drugs, such as rifampin and some seizure medications can do likewise, by boosting the quantity of cytochrome P450 enzymes produced. Proton pump inhibitors are also metabolized by P450 enzymes. Using an “artificial liver” system in a test tube, Kevin Akers of the U.S. Army Institute of Surgical Research, San Antonio, Tex., et al. added proton pump inhibitors to slow down metabolism of voriconazole. “PPIs increased the voriconazole remaining at the end of the one-hour test period by up to 51%,” says Akers. “We showed that PPIs could be used to boost voriconazole by interfering with the P450 enzymes. Knowledge of this phenomenon could be critical to saving patients with life-threatening fungal infections. But clinical trials are needed to confirm this effect.”

NEW IN ASM JOURNALS

Superior Whole-Genome Sequencing for Serotyping E. coli

“The accessibility of whole genome sequencing (WGS) presents the opportunity for national reference laboratories to provide a state-of-the-art public health surveillance service,” Claire Jenkins, of Public Health England, London, writes in a review article. “The replacement of traditional serology-based typing of [E. coli] by WGS is supported by user-friendly, freely available data analysis Web tools,” she adds, pointing to an accompanying article (doi.org/10.1128/JCM.00008–15) which “describes Serotype-Finder, an essential guide to serotyping E. coli in the 21st century.”


NEW IN ASM JOURNALS

MALDI-TOF Demonstrates Speed, Accuracy, in Blinded Trial

In the case of a release of highly pathogenic bacteria (HPB), fast, accurate, reliable diagnostics are urgently needed. MALDI-TOF mass spectrometry is demonstrating its competence and relatively low expense in this regard. Daniela Jacob of the Centre for Biological Threats and Special Pathogens, Robert Koch Institute, Berlin and investigators from 11 partner institutions from nine European countries demonstrate as much in this exercise in which ten distinct microbial samples, including Bacillus anthracis, Brucella canis, and Yersinia pestis, were characterized under blinded conditions. Average identification accuracy reached 93%. The work shows that MALDI-TOF mass spectrometry works for some of the most dangerous pathogens on the select agents list, and that the Europeans lead the US in adopting this technology.


NEW IN ASM JOURNALS

MAbs Show High Neutralizing Activity Towards H7N9

Influenza A virus H7N9 is an emerging global health concern, causing around 35% mortality in humans. Jianmin Wang of the Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, et al. have characterized two human monoclonal antibodies, which they show possess high neutralizing activity towards this virus. The researchers screened for the antibodies by establishing Fab antibody phage libraries derived from patients who had recovered from H7N9 infections. As of September 2014, 454 cases, including at least 171 deaths, had been reported.

Rethinking the Tree of Life

Even though lateral gene transfers tend to undermine this beloved metaphor, the underlying theory of evolution is very much intact

W. Ford Doolittle

Two decades ago, rumors began to spread that something was seriously wrong with the universal Tree of Life (TOL). Since the middle 1960s, evolutionists had been comparing molecular sequences—first proteins, then ribosomal RNAs, then protein-coding genes, and later genomes—to reconstruct evolutionary relationships. Tacit assumptions in this pursuit, called molecular phylogenetics, were that all genes would tell pretty much the same story, enabling us to trace back through a series of branchings to some single last universal common ancestor (LUCA).

However, in the 1990s, some evolutionists realized that for prokaryotes, at least, such assumptions might not be safe. Because of lateral gene transfers (LGT), analyses of different genes can yield different trees. Moreover, nothing can guarantee that any gene will have escaped being transferred sometime during four billion years of life. Several of us thus began to ask if it would still be possible to construct a universal TOL and whether such a tree would be meaningful.

Tree Huggers versus Bashers

That two-decade debate between those who answer yes to both those questions (the “tree-huggers”) and those who answer no (the “tree-bashers”) leaves us with a conceptual conundrum. We can construct what looks like a TOL, but whether it is valid depends on what we want that concept to be, more a matter of philosophy than biology. Here I ask whether the TOL is (i) what Darwin meant it to be, (ii) proof of the theory of evolution, (iii) a tracing of the history of cells and species, (iv) singly rooted, (v) a sensible framework for systematics, or (vi) essential in the battle against creationism.

My response, perhaps predictably, is none of the above six, despite there being some value in each possibility. My reservations deal mainly with the prokaryote part of the TOL. For one thing, LGT is surely less frequent in complex multicellular plants and animals, especially those with differentiated germ lines. Although there are reliable reports of LGT among unicellular eukaryotes, especially phagotrophic protists, prokaryotes comprise the majority of living things on this planet, excluding viruses. So for the TOL, accommodating prokaryotes and LGT looms as the most critical challenge.

Considering the Six Possibilities: Darwin’s Version

Biologists were drawing trees centuries before Darwin, and similar efforts to organize physical observations or concepts into categories and subcategories go back at least as far as the Greek philosophers. Assigning organisms into hierarchical schemes based on phenotypic similarities and differences—branching trees—seems natural. Thus, for example, all birds are more like each other than any is to any fish, and vice versa, while birds and fishes are more closely related to each other than to flowering plants. In biological systematics we argue about what the truth is, but not

SUMMARY

➤ Abundant lateral gene transfers complicate efforts to construct a phylogeny for prokaryotes that is at once meaningful and universal.

➤ An independent hierarchical classification based on phenotype, if available, would show many disagreements with that based on popular gene phylogenies, at all levels.

➤ The tree of life cannot by itself be taken as proof of the theory of evolution because there are other ways to explain hierarchical classifications.

➤ In defending the theory of evolution, some experts conflate “common ancestry” with “common ancestor.”

➤ Newer network methods may more accurately represent evolutionary relationships than do trees.
about whether there is one. Before 1859, why any biological classification should be true was a philosophical or theological matter. For Christians it was easy: an orderly classification reflected the orderly mind of a Creator.

Possibility One: a Naturalistic Hypothesis

Darwin did not set out to challenge Christianity, but he did seek a non-supernatural explanation for the orderliness and seeming naturalness of biological classifications. He found it in evolution. “All true classification is genealogical,” he wrote in On the Origin of Species. Moreover, he thought the pattern would be tree-like all the way down: “The affinities of all beings of the same class have sometimes been represented by a great tree. I believe this simile largely speaks the truth . . . [a ‘great tree,’ whose] ramifying branches may well represent the classification of all extinct and living species in groups subordinate to groups.”

Those comments are part of what Eric Bapteste and I call Darwin’s “Tree of Life Hypothesis (TOLH).” He and other systematists saw a tree-like pattern of natural classification based on phenotype, and he inferred an underlying tree-like process producing that pattern. Darwin called this process “descent with modification,” but we just call it “evolution.” The TOLH is a hypothesis rather than a fact because a branching evolutionary process is not the only way to explain tree-like classifications (Fig. 1).

Although the Tree of Life Hypothesis should be testable, for many prokaryotes, it is not. For them, we have no widely accepted “natural classification” other than that based on ribosomal RNA (rRNA) sequences, widely taken to represent the underlying evolutionary process. Of course this pattern and process agree, because they are part of a circular claim. But an independent hierarchical prokaryotic classification—like earlier ones for animals and plants based on phenotypic similarities and differences—would often differ from one based on the rRNA tree, sometimes drastically.

When trying to infer phenotype from genes in any genome, this problem shows up at all taxonomic levels. With species, there can be disagreement between phenome and strain position in an rRNA-based phylogeny. At the phylum level, there are instances like the Thermotogales, which are sister taxa to Aquificales based on ribosomes, but fall within Firmicutes with the majority of their other genes. And, at the domain level, the
widely accepted closer relationship of Archaea and eukaryotes is based only on a minority of genes: the majority show a bacterial/eukaryotic affinity.

**Possibility Two: Proof of the Theory of Evolution**

Simply expanding hierarchical classification by adding more taxa and improving tree-construction algorithms does not prove the theory of evolution. Hierarchical classification is a fact of nature to be explained, and it cannot logically be then re-employed to prove that explanation. The circularity of such reasoning is embedded in *The Origin*, as the late Alec Panchen of the University of Newcastle and Niles Eldredge of the American Museum of Natural History pointed out decades ago. Thus it is the convergence (consilience) of many independent lines of evidence from systematics, phylogenetics, molecular biology, biogeography, and developmental biology that so robustly supports the modern theory of evolution, not any one alone.

What most distinguishes Darwin’s TOLH from the “orderly mind of the Creator” theory? The “ancestral” nodes deep within the great tree that Darwin embraced as a “simile” correspond to ancestors within a historical sequence. God’s creating all taxa in a few biblical days, however, leaves no room for such an extended history and no ancestors.

Some nontheologically motivated tree bashers also question the extent to which ancestral nodes in the TOL correspond to real ancestral taxa. Two bacterial species A and B that exchange genes with each other frequently will inevitably come to resemble each other closely in gene composition or gene sequence even if they share no common ancestor. Treeing methods will show A and B as “sister” taxa (Fig. 1). For this second and fully logical reason, constructing trees does not by itself prove Darwin’s theory.

**Possibility Three: Tracing the History of Cells and Species**

Tree huggers generally admit that LGT is far more pervasive than was thought when molecular phylogenetics was conceived. Because of LGT, gene trees will disagree and there can be no unambiguous single “tree of genomes.” However, because genomes replicate only within organisms, there is in principle a tree of organisms and cells, comprising all speciation events and (for asexual lineages) all cell divisions back to the beginning of time. Tree bashers might protest that this concept privileges some cellular processes over others, but it is not incoherent.

We might construct a presumptive tree of species and cell divisions, in several complementary ways. First, we could build the tree with “core” genes that are present in all or most genomes. Ribosomal RNA, ribosomal protein, and other translation-related genes are favored for this building process not only because they are universal but also because they appear to be difficult to transfer over substantial phylogenetic distances. Moreover, it was rRNA on which the late Carl Woese based his groundbreaking microbial phylogeny. However, even if we could be sure that ribosomal and other core genes never transfer, such genes are very few. One attempt to construct a universal TOL from 31 core genes was famously derided as “the Tree of One Percent.”

Second, we might construct trees on the basis of shared gene content, without attention to sequence divergences within gene families. In following this approach, for example, Thermotogales would be nested within the Firmicutes. Third, we might try super-tree, super-matrix, or consensus approaches to reconcile incongruent individual gene trees, forcing them into a minimally conflicting structure, which might be thought of as the “central tendency” of the data. Fourth, newer hybrid methods aim to reinforce core or supertree approaches by recognizing that LGTs at the base of clades make excellent shared characters for defining them.

All these approaches might work despite rampant LGT, if LGT were random, occurring at similar frequencies regardless of the evolutionary distance between or ecological preferences of donors and recipients. However, LGT is not random. Within species, homologous recombination can be very frequent, leading trees for strains to differ gene by gene. Two routes for between-species LGT, conjugation and transduction, typically show some degree of host specificity, while transformation should be more difficult the greater the phylogenetic distance between donor and recipient, because of divergence in informational machinery. The consequences of such a “phylogenetic bias” on LGT might be seen as harmless or beneficial to tree-building, with LGT...
reinforcing the true evolutionary signal. Still, such trees are at best “fuzzy”.

Ecological bias is a more serious problem. LGT is more frequent between donors and recipients that live in the same sorts of places and do similar things. None of the four methods is immune to this bias, and there will be instances where gene-based reconstructions do not accurately reflect the history of speciation.

Possibility Four: Singly Rooted

The last sentence of the first edition of The Origin begins, “There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one . . .” This last small equivocation notwithstanding, most scholars see that the Tree of Life had but a single root.

Woese imagined something more inchoate, with Bacteria, Archaea, and Eukarya arising as cellular lineages independently from a “progenote” state. If we define life as replicating information and see it emerging first at the level of RNA, it is possible that many forms rather than one cooperated before cellular life took off. However, most tree-huggers talk in terms of a single last universal common ancestor, and some but not all imagine it to be a single cell.

Rampant LGT means that most if not all the genes in such a cell will have been lost or replaced by homologs or nonhomologous genes with the same or different functions, unless some genes can never be lost, gained, or replaced. Thus, LUCA’s genes are not directly necessarily ancestral to contemporary members of the gene family to which they belong. Even were it sensible to imagine a single root to the TOL we cannot be sure what genes the organism corresponding to that root had or of anything about its phenotype.

Possibility Four: a Sensible Framework for Systematics

Systematics is as much a legalistic practice as a science. In principle it can be divorced from evolutionary theory, and in the 1950s and 1960s pheneticists and numerical taxonomists insisted that it should be. Phenetic classifications, based on assessing overall similarities objectively, are unquestionably useful in inferring evolutionary (cladistic) relationships, and branching processes. But if classifications already incorporate inferences about evolution, we are trapped in circular reasoning. Indeed, Darwin’s TOLH is that branching evolution explains tree-like phenetic classification, not that these are identical, conceptually or in practice. However, since Darwin we tend to assume, simplistically, that proper classifications are genealogical. For many, “classification” and “phylogeny” are synonyms.

LGT makes genealogy less tree-like and requires that we again separate phenetics from cladistics. Indeed, some argue that networks rather than trees should be the basis of systematics. It is hard to beat dichotomously branching hierarchies, however, and most of us would probably be uncomfortable saying that Thermotoga maritima is not only a member of the phylum Thermotogae but also of the phylum Firmicutes. Bergey’s Manual adopted rRNA phylogenetics as the “backbone” for its taxonomy at higher ranks, and this system seems the best bet when facing discoveries of new life forms and methodological innovations. Such enshrinement should nevertheless not be taken as a guarantor of the truth, or evidence that there is only one simple truth about relationships.

Possibility Six: Essential in the Battle against Creationism

Several biologists who defend the theory of evolution argue as if the TOL were essential for that defense. For Creationists, “organisms would not have common ancestry, but would simply result from an instantaneous creation of forms designed de novo to fit their environments,” notes Jerry Coyne at the University of Chicago. “Under this scenario, we wouldn’t expect to see species falling into a nested hierarchy of forms that is recognized by all biologists.” Richard Dawkins, in an amusing exchange with Craig Venter, seems to hold a similar view (https://www.youtube.com/watch?v=MXrYhINutuI).

They and other experts conflate “common ancestry” with “common ancestor.” The analogous mistake in human evolution would be to assume that because all men might trace their ancestry by their Y chromosomes back to one single “Y-chromosome Adam” and all women might trace their mitochondria back to a single “mitochondrial Eve,” that these two were a couple. Current thinking is that they lived in different populations thousands of years apart. Moreover, our non-Y,
nonmitochondrial autosomal alleles trace back to still different individuals. Because of sex and recombination, common ancestry does not mean that there is a single common ancestor or ancestral couple. Similarly, because of LGT, there was not a single cell or species in which the last common ancestors of all genes in prokaryotes were present. Moreover, there will always be nodes, but these need not always be ancestors. The “nested hierarchy of forms that is recognized by all biologists” is not proof of process. Such a proof is not needed to counter the claims of Creationists. All we need to assert is that genetic and ecological processes and forces of which we have by now a very good understanding are adequate when extrapolated over three or four billion years to explain the adaptedness and diversity of life on this planet. Our explanatory toolkit is very robust and, though the theory of evolution is more complex and nuanced than Darwin imagined, he would surely be pleased our progress in elaborating it.

Conclusion

Tree huggers and many tree bashers accept that the TOL is a robust or “good-enough” metaphor and a logical basis for universal classification. However, it may be inappropriate in many specific contexts. Sometimes the pattern will be reticulate and sometimes tree-like, and the hierarchical level of analysis matters. There logically is a single tree of animal phyla, but within (sexual) animal species there is no single tree of individuals, nor is there one of genomes or genes (because of recombination). Only at the level of nucleotides is there again in principle only one tree. Much of the heat in the debate over the TOL comes from conflating the “Tree of Genomes,” which does not exist, with the historical tree of cells and species, which might. Molecular phylogenetics encouraged this conflation. It is not necessary to make the truth of a TOL a bulwark in our defense of the theory of evolution. Newer “network” methods may more accurately represent evolutionary relationships, though it is hard to see how they will ever achieve the convenience of hierarchical schemes for organizing knowledge and identifying species. We might be wise to relax the requirement that “all true classification is genealogical.” The truth is more complex than Darwin knew or could have known.

Suggested Reading

Applying the Restaurant Hypothesis to Intestinal Microbiota

Anaerobes in mixed biofilms degrade polysaccharides, sharing locally prepared sugars with facultative anaerobes that also colonize the intestine

Tyrrell Conway and Paul S. Cohen

As in other ecosystems, competition for resources drives the microbial community structure within the intestine. For so many species to coexist within the intestine, each uses at least one limiting nutrient better than all others, according to the late Rolf Freter of the University of Michigan and his collaborators. Accordingly, if residents within that community consume the nutrients that an invader needs, this potential pathogen will not find essential nutrients and will fail to become established.

What if this competition for nutrients was understood well enough to prevent pathogens from gaining a foothold in the first place? We make a case for the “restaurant hypothesis” to explain how *E. coli* becomes stably colonized in nutrient-defined intestinal niches. We postulate that *E. coli* resides in “restaurants” where it grows on sugars that are served locally by polysaccharide-degrading anaerobes in mixed biofilms. Invading pathogens must compete successfully with the resident microbiota to enter into their own restaurant, or they are eliminated. This barrier effect of the resident microbiota is termed “colonization resistance.”

What Happens after Bacteria Arrive in the Intestine

To establish itself within the gut community, *E. coli* typically depends on exiting lag phase and entering growth phase. Freter, who sought to understand how competition for resources within the intestine leads to stable multispecies communities, postulated that each species occupies its own nutrient-defined niche. By establishing stable multispecies communities in continuous-flow cultures and in streptomycin-treated mice, he ascertained that competition for nutrients is the key mechanism controlling these microbial populations. His nutrient-niche hypothesis is widely accepted today, but does not accommodate the restaurant theory.

Prominent nutrients within the colon include polysaccharides in undigested fiber, epithelial cell debris, and mucus. The relative absence in *E. coli* of genes encoding polysaccharide hydrolases led us to suspect that *E. coli* depends on polysaccharide-degrading anaerobes to furnish it with mono- and disaccharides. Indeed, polysaccharide-degrading cells of *Bacteroides thetaiotaomicron* also provide both *Salmonella enterica* serovar Typhimurium and *Clostridium difficile* free fucose and sialic acid within the intestines of mice, according to Justin Sonnenburg at Stanford University and his colleagues.

That example and others like it support our restaurant hypothesis, which predicts that polysaccharide-degrading anaerobes provide free sugars, for which facultative anaerobes such as *E. coli* and *Salmonella* compete locally in mixed bio-

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**SUMMARY**

- When introduced into streptomycin-treated mice, *Escherichia coli* envZ mutants that grow slowly in vitro on intestinal mucus, despite high numbers of their wild-type parent, use galactose to colonize a different intestinal niche.
- *Bacteroides thetaiotaomicron* bacteria degrade polysaccharides, providing fucose and sialic acid to invading pathogens such as *Salmonella enterica* serovar Typhimurium and *Clostridium difficile*, allowing them to colonize the intestine.
- According to the restaurant hypothesis, polysaccharide-degrading anaerobes establish microhabitats within the large intestine mucus layer, supplying sugars to nearby facultative anaerobes.
- The growth patterns of *E. coli* strains within intestines seem to track what happens in mixed biofilms.
films. Not so long ago, no one could say for certain what E. coli grows on within the intestine. Meanwhile, we determined that E. coli depends on glycolysis, the tricarboxylic acid (TCA) cycle, and the Entner-Doudoroff pathways of central metabolism and that it respires oxygen, nitrate, and fumarate.

More specifically, we learned that E. coli grows rapidly on cecal mucus, but not on luminal contents or feces and, therefore, must penetrate the mucus layer where it is interspersed with other members of the resident microbiota (Fig. 1). From comparing commensal and pathogenic E. coli strains, we learned that, despite using the same nutrients in vitro, they use different subsets of available nutrients in the intestine. For example, when streptomycin-treated mice are colonized with one E. coli strain and then fed low numbers of a different strain, the second strain can grow to higher numbers in the intestine. However, if that strain essentially is the same as the first strain and can be identified by having a different antibiotic resistance marker, it is eliminated. Thus, different E. coli strains occupy distinct niches in the intestine that are defined by the nutrients they use.

**Distinct Types of Competition for Nutrients**

E. coli competes for nutrients in the intestine in at least three ways. First, a strain might consume nutrients that no other community member uses. Second, one strain might grow faster than other strains on a particular nutrient. For example, when E. coli K-12 strain MG1655 adapts to the mouse intestine, nonmotile flhDC deletion mutants appear 3 days after feeding and account for approximately 90% of the total population within 10 days. FlhDC is the master positive regulator of the flagella regulon, which contains nearly 40 genes, and also controls genes involved in galactose and ribose transport, as well as the Entner-Doudoroff pathway and the TCA cycle. These flhDC mutants had a striking colonization advantage over the parent strain, presumably because they overexpress catabolic pathways that yield 15–30% faster growth in vitro on sugars and cecal mucus.

Third, a strain might associate with an anaerobe that releases its preferred nutrients locally. Why did the superior flhDC mutants not out-compete the 10% of the population that remained motile? We found a second class of envZ missense mutants, missing a histidine kinase. That enzyme belongs to the envZ/ompR two-component signal transduction system that modulates gene expression in response to osmolarity. These regulated genes include flhDC, the porin genes ompC and ompF, and several more genes encoding outer membrane proteins. Remarkably, rather than growing faster, these envZ mutants grow more slowly on mucus and several sugars, yet they are better colonizers than the wild type.

How can this envZ strain grow more slowly and yet be a better colonizer? To characterize these mutants, we transferred the E. coli MG1655 envZ allele into E. coli Nissle 1917, which surprisingly grows 50% slower in vitro on mucus and as much as 30% slower on several sugars, yet is a 10-fold-better colonizer than is its wild-type parent.

Thus, both the E. coli MG1655 and Nissle 1917 envZ mutants appear to use galactose to colonize a second intestinal niche either not colonized or colonized poorly by their wild-type parent strains. According to the restaurant hypothesis, we postulate that the envZ mutants obtain the galactose they need locally via specific interactions with anaerobes within mixed biofilms, in niches that are not occupied by their wild-type parents.

**FIGURE 1**

Fluorescent in situ micrograph of a thin slice of the cecum from a streptomycin-treated CD-1 mouse showing E. coli MG1655 (red) interspersed with resident anaerobes (green). A portion of an epithelial cell is indicated by Ep. (Bar, 5 μm.)
Role of Biofilms in the Intestine

Although biofilms occur in many environments, little is known about their role in the intestine. Can stable biofilms be maintained in the intestine, where transit times are brief compared to the timescale of biofilm development? Simple logic would say no. Nevertheless, the speed of plasmid transfers between *E. coli* strains in the intestine suggests that they reside in biofilms in the mucus layer, which resembles a secreted biofilm matrix (Fig. 2).

The growth patterns of *E. coli* strains within intestines, with different anaerobes appearing to supply those different strains with specific nutrients, seem to track what happens in mixed biofilms. Apparently, *E. coli* strains are provided with particular sugars locally, rather than from a mixed pool of sugars that would more likely be available to all species with access to that pool. Thus, we picture different *E. coli* strains interacting physically and metabolically with different anaerobes, a view that helps to explain why different strains of the same species follow different nutritional programs in the mouse intestine despite following identical nutritional programs in vitro. This hypothesis could also explain why some *E. coli* strains grow more slowly in vitro on mucus, yet are better colonizers than their parents. It appears that they have a higher affinity for particular biofilm binding sites.

How does this hypothesis apply to pathogenic strains replacing established strains in the intestine? Resident microbiota members, ordinarily a barrier to such invaders, belong to mixed biofilms, taking up nutrients as they are released by adjacent polysaccharide-degrading anaerobes (Fig. 3). However, the biofilms doubtlessly leak
small amounts of those sugars, meaning they would likely be available to invading *E. coli* or other strains, which would compete directly with planktonic residents of the intestine that are also consuming those leaked nutrients.

This scenario could explain how a newly ingested planktonic invader could compete with planktonic residents within a “Freret-like” niche, in which nutrients are mixed and equally available to invaders and planktonic residents alike. If an invasive strain could remain long enough in the intestine, it might then become stably colonized within that environment, presumably by becoming a member of a newly formed restaurant.

**Glimpses of Microbes within the Intestine**

How are microorganisms situated within the intestine? In thin slices of mouse cecal tissues, *E. coli* cells are interspersed between resident anaerobes in what appear to be mixed biofilms, according to fluorescent in situ hybridization (FISH) microscopy. Differences in cell morphologies of the resident microbes reflect the diversity of this anaerobic community (Fig. 1). How these separate communities might be organized within these biofilms is not known. Conceivably, immediately adjacent bacteria interact in very specific ways with one another.

We must await technologies that can truly reveal the degree and nature of any specific species-species interactions. One promising approach involves single-cell, in situ gene expression analysis to assess the physiological state of colonized bacteria. Another potentially helpful approach would be to undertake nano-scale mass spectrometry to reveal nutrient flows between adjacent members of microbial communities.

In the meantime, we can only approximate such activities from population-scale studies. In general, they suggest that, once *E. coli* cells reach the large intestine, they enter the mucus layer, using nutrients there to become a stable part of the intestinal community. Meanwhile, different *E. coli* strains display different nutritional programs within the intestine. Whether a specific *E. coli* commensal strain uses the same nutrients when it is the only strain or one among many other strains competing for nutrients is not known.

Metabolic flexibility could be a key requirement for successful co-colonization by several *E. coli* strains. However, the restaurant hypothesis can explain long-term, mixed-strain colonization without invoking metabolic flexibility. Thus, each commensal *E. coli* strain may reside as a sessile member of a mixed biofilm in the intestine, each separately obtaining nutrients locally, rather than from a perfectly mixed pool of such nutrients. When animals are stably colonized with one *E. coli* strain and then ingest a pathogenic strain, planktonic members of the resident strain that escape the mixed biofilm will compete directly with the invading pathogen for nutrients. Because enteric pathogens must grow to cause infections, this nutritional framework can help to shape a microbiota that might be a
more effective first-line defense against such infections.

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SUGGESTED READING


Developing Research-Based Undergraduate Microbiology Curricula

Redesigning undergraduate microbiology courses will better enable students to understand and solve problems within this discipline

Rachel E. A. Horak, Susan Merkel, and Amy L. Chang

Despite being an important part of the mission for colleges and universities, teaching is often given short shrift. Designing courses is particularly challenging for new faculty members, who often get little training as graduate students or postdoctoral fellows on how to design or teach courses. Increasing diversity in classrooms, large class sizes, and the fast pace of scientific discoveries serve to make teaching even more challenging.

In addition, academic rewards, including promotions, salary increases, and tenure, tend not to credit faculty members for their effective and innovative teaching skills, putting further time constraints on them as they balance research, teaching, and service demands.

How can faculty members cope with teaching challenges? When designing a new course or revising a curriculum, instructors can expect to address several important questions, including:

- What should my students learn?
- How will I know if my students learned what I wanted them to learn?
- What are the best modes to promote learning?

Findings in the recently emerged field of discipline-based education research (DBER) can help to answer these questions. DBER investigates learning and teaching from a perspective that reflects a particular discipline’s priorities, worldview, knowledge, and practices. A discipline-based approach to designing curricula was presented in the 2011 AAAS/NSF report *Vision and Change in Undergraduate Biology Education: A Call to Action*. It lists core competencies, skills, and concepts, and recommends the overarching goal is for students to apply what they learn to solve authentic problems within the discipline.

Because professional societies such as ASM can set teaching standards within their respective disciplines, they are well suited to promoting changes within academia. The ASM Education Board has developed a range of resources and training opportunities that are based on educational research to help educators in microbiology redesign their undergraduate courses while making teaching experiences more effective.

What Students Should Be Learning

When faced with the task of designing a course, many instructors rely on textbooks for structure, and focus on content rather than skills and problem solving. DBER studies indicate that this approach to designing courses promotes lower-level thinking skills and rote memorization instead of more important themes and concepts.

A discipline-based approach to designing curriculum was presented in the 2011 AAAS/NSF report *Vision and Change in Undergraduate Biology Education: A Call to Action*. It lists core competencies, skills, and concepts, and recommends the

**SUMMARY**

- ASM has developed *Curriculum Guidelines for Undergraduate Microbiology* relying on discipline-based education research, which educators are using, together with other ASM resources, to design effective microbiology courses.
- Aligning course learning outcomes, assessments, and instruction promotes the understanding of core concepts and the development of skills that expert microbiologists need.
- Frequent and varied assessment provides evidence of student learning.
- Student learning greatly improves when educators use research-based instructional methods and course structures.
“understanding by design,” also called “backwards design,” framework to develop course curricula. In this, instructors first consider what skills and concepts are important for microbiologists and then establish learning goals for their students to meet. Instructors then collect evidence to determine if their students are meeting the goals, and then develop teaching and learning activities. The process is iterative and synergistic, with each step informing the next.

ASM revised its Curriculum Guidelines for Undergraduate Microbiology (asm.org/educators) in 2012 to make them compatible with this discipline-based approach to course design (Fig. 1). The effort began with a task force surveying the microbiology education community and then developing a curriculum framework consisting of 4 scientific-thinking skills, 7 laboratory competencies, and 27 fundamental concepts in microbiology. Instructors can work from these fundamental concepts to design their courses (Fig. 1, green). A concrete example of a microbiology lesson is diagrammed in Fig. 2.

In fall 2014, we surveyed the microbiology education community to learn how widely these new guidelines were being implemented and how useful they were to instructors. An overwhelming majority (80%) of more than 350 educators who responded to the survey said they had heard of the new guidelines; 48% of them had used the Guidelines to redesign an existing course, 13% designed a new course, and 3% designed a new concentration or major. Educators were using the Guidelines with both microbiology majors and pre-health sciences students and for courses such as general biology, virology, immunology, public health microbiology, and biotechnology. The biggest challenges to implementing the guidelines include lack of time, financial resources, and resources.
The next design step calls for developing learning outcomes, which are statements that indicate what skills students should master during a course. Those skills encompass a hierarchy of learning, ranging from remembering or understanding to applying, analyzing, evaluating, and creating. Taken together, the learning outcomes comprise an overall map for the course because they set directions for learning. Writing effective learning outcomes is a challenge. To help in meeting this need (Fig. 2, Table 1), ASM posted a list of 165 example learning outcomes on its website (http://www.asm.org/images/Education/FINAL_Learning_Outcomes_w_title_page.pdf).

Determining How Well Students Are Learning

Determining what your students learned is called assessment. “Summative” assessments measure what students know or can do at the end of a course, and they include exams, group projects, lab reports, and written papers. Effective summative assessments are ones that resemble “real-world” tasks, allow students more than one way to demonstrate knowledge, and reflect learning experiences. One example of an authentic assessment, having students write research proposals, provides them the opportunity to develop scientific-thinking skills by writing testable hypotheses and designing experiments and methods.

“Formative” assessments are used during the course process to help each student improve his or her understanding of the material being taught. Formative assessments provide feedback to instructors and students about whether specific skills are being gained. The many different types of formative assessment include one-minute essays, think-pair-share exercises, and “clicker” questions that poll students within a classroom. Additional examples of formative assessments are provided in Classroom Assessment Techniques by Thomas A. Angelo and K. Patricia Cross (1993).

The ASM Education Board is developing a peer-reviewed collection of clicker questions for
introductory microbiology courses. Called the Student Learning Assessments in Microbiology Database (SLAMD), the collection features questions that can be used as formative assessments for concepts in the ASM Curriculum Guidelines. SLAMD is currently soliciting questions for an e-publication, scheduled for release in 2016.

Concept Inventories help instructors determine how well students really understand concepts that are important within a particular discipline. These short tests typically contain 20 to 25 multiple-choice questions that are thoroughly evaluated for their reliability in assessing what students have learned. Concept inventories typically are administered at the beginning and/or end of a course, and can be used to assess the effectiveness of different instructional strategies.

Undergraduate educators now can draw on concept inventories for a range of topics in physics, engineering, and chemistry but have fewer

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**TABLE 1. ASM-sponsored professional development opportunities and resources that support faculty in implementing the ASM Curriculum Guidelines and research-based instructional strategies**

<table>
<thead>
<tr>
<th>Event/Resource</th>
<th>Description</th>
<th>Date available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional development events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M(icro)OOC webinar</td>
<td>A webinar series about topics related to microbiology teaching</td>
<td>Ongoing; archived webinars available now</td>
</tr>
<tr>
<td>ASM Conference for Undergraduate Educators (ASMCUE)</td>
<td>Four-day interactive conference for educators with many pedagogy sessions</td>
<td>Yearly</td>
</tr>
<tr>
<td>ASM Science Teaching Fellowship</td>
<td>Four-month online course to prepare early-career faculty for teaching positions</td>
<td>Yearly</td>
</tr>
<tr>
<td>Biology Scholars Program</td>
<td>Year-long, primarily web-based program for national leadership development</td>
<td>Yearly</td>
</tr>
<tr>
<td>Resources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASM Curriculum Guidelines for Undergraduate Microbiology Education</td>
<td>Recommended curriculum for microbiology course or program of study. Includes concepts, competencies, and skills</td>
<td>Available now</td>
</tr>
<tr>
<td>ASM Curriculum Guidelines Learning Outcome Examples</td>
<td>A collection of learning outcomes for undergraduate microbiology; written by the ASMCUE community</td>
<td>Available now</td>
</tr>
<tr>
<td>ASM Guidelines for Biosafety in Teaching Laboratories</td>
<td>A comprehensive guidebook of uniform biosafety recommendations for working with microorganisms in the teaching laboratory</td>
<td>Available now</td>
</tr>
<tr>
<td>Journal of Microbiology &amp; Biology Education: Curriculum and Tips and Tools</td>
<td>Peer-reviewed collection of microbiology classroom activities</td>
<td>Available now</td>
</tr>
<tr>
<td>ASM MicrobeLibrary Curriculum Archive</td>
<td>Eighty-five peer-reviewed microbiology classroom activities that promote active learning</td>
<td>Available now</td>
</tr>
<tr>
<td>MicrobeLibrary resources</td>
<td>Peer-reviewed collection of microbiology-related images, videos, animations, and laboratory protocols</td>
<td>Available now</td>
</tr>
<tr>
<td>CourseSource</td>
<td>Peer-reviewed collection of microbiology classroom activities</td>
<td>Available now</td>
</tr>
<tr>
<td>Student Learning Assessment in Microbiology Database (SLAMD)*</td>
<td>Peer-reviewed, multiple-choice questions that assess concepts in the ASM Curriculum Guidelines</td>
<td>2016</td>
</tr>
<tr>
<td>Microbe, 2nd ed.*</td>
<td>Undergraduate microbiology textbook that will promote deep learning of the concepts in the ASM Curriculum Guidelines</td>
<td>2016</td>
</tr>
<tr>
<td>Concept Inventories General Microbiology and Microbiology for Health Sciences</td>
<td>Nationally tested and validated instruments to assess learning of concepts in the ASM Curriculum Guidelines</td>
<td>2016–2017</td>
</tr>
</tbody>
</table>

*a In development.*
options for biology, including one microbiology-related concept inventory: The Host-Pathogen Concept Inventory. To provide more options, ASM is supporting the development of two concept inventories, one for general microbiology students and one for allied health students, both of which assess learning of concepts presented in the ASM Curriculum Guidelines. These two inventories are expected to be ready for distribution by 2016 or 2017.

**Switching to Better Instructional Modes**

Instructional strategies backed by educational research are more effective for conveying concepts to students than are traditional lectures, according to DBER studies. Such strategies include in-class peer instruction, problem-based learning, use of clicker questions, and intensive and deliberate skill practice. When instructors conduct any type of active learning, course failure rates decrease by 55% and performance on concept inventories significantly improve, according to a Scott Freeman of the University of Washington and his colleagues, based on their meta-analysis of more than 225 educational research studies.

Educators now can evaluate their use of research-based instructional strategies with an online, freely available instrument: the “Teaching Practices Inventory,” which was developed by Carl Wieman and Sarah Gilbert (*Microbe*, April 2015, p. 152 and May 2015, p. 203). This self-assessment inventory takes approximately 10 minutes and uses a scoring rubric to identify the

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**AUTHOR PROFILE**

**Horak: from Research in Submersibles and Teaching to Swimming and Coaching**

Moving from a lab bench to a desk was an adjustment for Rachel E. A. Horak, who likes to work with her hands in the lab and especially at sea. In 2014, Horak joined ASM in Washington as an education fellow, an experience that connects her with diverse microbiologists while expanding her skills, she says. “I had the opportunity to write a large grant proposal to the National Institutes of Health, gain online teaching experience, publish education-related manuscripts, and learn about biology education research. The [ASM fellows] program is perfect for microbiologists who want to explore science careers outside the laboratory.”

Before moving to Washington, Horak studied water column nitrification and denitrification, as a postdoctoral researcher at the University of Washington in Seattle. “I spent 130 days at sea from 2012–2013,” she says. “Basic ocean research is of increasing importance in this era of anthropogenic climate change.”

Horak, 36, was born in Texas and moved to Northern Virginia in 1984. Her mother, now retired, was a public school preschool teacher for special needs children, and her father is a professor at Georgetown University. Her brother is an assistant principal at a Northern Virginia elementary school, and her half-siblings are in college. “Most influences on my science career started at Davidson College,” where she received a B.S. in biology in 2000, she says. “I had wonderful biology professors, which is what inspired me to major in biology.” She received her M.A. in 2004 from the College of William & Mary, and her Ph.D. in 2010 from the Georgia Institute of Technology.

“I had the fortunate opportunity to do three dives in manned research submersibles,” Horak recalls. “I was humbled and partly scared. Incredible research opportunities like these are part of what keeps me motivated to continue science research.” She also loves teaching. For ASM, she conducted a series of webinars about teaching; earlier, she taught freshman seminars and courses in astrobiology at the University of Washington.

Horak was a serious competitive swimmer from age 7, and she continues to compete as an adult. She started coaching young swimmers at 19, and served as an assistant swim coach at Davidson, whose women’s team won four conference championships while she was on it. “My best events were in sprint freestyle and backstroke,” she says. “The challenges of competitive swimming taught me perseverance, dedication, and time management—all very important life lessons.” Coaching also helped her as a teacher. “The same skills that I needed to help young swimmers . . . are necessary to help biology students develop scientific thinking skills, and writing and communication skills.”

She met her husband Tim, a postdoctoral researcher at the National Institutes of Health, while they were both at Georgia Tech. “My husband and I are sports fanatics and are dedicated to our fitness,” she says. They also are beer and wine “fanatics,” and spend their vacations visiting breweries and wineries. They are expecting their first child later this year. In the meantime, they dote on their black Labrador retriever mix, River, and two ferrets, Blitz and Dolce.

Marlene Cimons

Marlene Cimons lives and writes in Bethesda, Md.
extent to which an educator uses instructional modes that improve student learning. They suggest that this inventory could also be used to evaluate teaching skills for faculty merit reviews.

The best way to foster student understanding of core concepts and skills is to align instruction with outcomes and assessments. For example, if the learning outcome involves students designing experiments, then the assessments and instruction should provide students with practice and feedback in experimental design. Much as it takes training and practice to learn a new laboratory technique, it takes training and practice for educators to learn how to apply research-based teaching and active learning techniques in classrooms. The ASM Education Board sponsors many Web-based and face-to-face professional development opportunities to assist educators in learning how to employ these strategies (Table 1).

**Perspective**

Discipline-based education research provides insights that can help our students master core microbiology concepts and skills. The ASM Curriculum Guidelines embrace national recommendations for reforming higher education across the sciences, and educators in microbiology can use those recommendations to develop curricula that are more effective for their students.

ASM has furthered these reforms through its peer-reviewed publications and by convening conferences and providing other types of support such as mentoring and recognition. For example, in 2005 the ASM Education Board began sponsoring the national Biology Scholars Program, which grooms leaders in science education reform. With so many important microbiology-related public issues at stake, it is critical that educators in this field use the best and most effective teaching methods available for preparing future microbiologists.

Rachel E. A. Horak is the Education Fellow and Amy L. Chang is the Education Director, both at the American Society for Microbiology Headquarters, Washington, DC. Susan Merkel is a Senior Lecturer in the Department of Microbiology at Cornell University, Ithaca, N.Y., and is the 2015 Carski Foundation Distinguished Undergraduate Teaching Award recipient.

**Author’s Note**

Rachel Horak and Susan Merkel are contributors to the undergraduate textbook *Microbe, 2nd ed.*, by ASM Press, currently in preparation.

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ASM has officially announced plans to launch two new interdisciplinary open-access journals, mSphere™ and mSystems™, in early 2016. Both journals will provide streamlined decisions along with short publication times, to ensure important findings are available to the scientific community as quickly as possible. Formal Calls for Papers are scheduled for September 2015.

*mSphere™* will be led by Founding Editor in Chief Michael Imperiale, who seeks to publish high-quality work that makes fundamental contributions to our understanding of the broad field of microbiology. *mSphere™* will also welcome papers in emerging areas that do not fit within the current scopes of ASM’s journals. The journal will undergo the same rigorous peer-review process as ASM’s nine primary research journals, with decisions made by working scientists.

Michael Imperiale is the Arthur F. Thurnau Professor and Associate Chair of the Department of Microbiology and Immunology at the University of Michigan Medical School and a member of the University of Michigan Comprehensive Cancer Center. His laboratory studies the molecular biology of small DNA tumor viruses, including BK polyomavirus, which can cause severe and sometimes life-threatening illnesses in transplant patients. He has authored more than 135 peer-reviewed journal articles and book chapters, and served as an editor of ASM’s *Journal of Virology* and *mBio* and associate editor of *Virology* and *PLOS Pathogens*.

**Jack Gilbert** will serve as the Founding Editor in Chief of *mSystems™*, a microbial systems journal that will capture work ranging from systems biology of individual microbes (consortia) to the systems analysis of microbial communities, including microbiome studies, microbial ecology, genomics, metagenomics, computational microbiology, and other work based on analysis of large datasets. The journal will welcome submissions from researchers who focus on the microbiome, genomics, metagenomics, transcriptomics, metabolomics, proteomics, glycomics, bioinformatics, and computational microbiology.

Jack Gilbert is Associate Professor in the Department of Ecology and Evolution and the Department of Surgery at the University of Chicago; Microbial Ecologist and Group Leader at Argonne National Laboratory; Senior Scientist at the Marine Biological Laboratory, Woods Hole; and Associate Director of the Institute of Genomic and Systems Biology. His research uses “omics” technologies to explore how microbial communities assemble themselves in natural and man-made environments. He currently manages the Earth Microbiome Project, an ongoing multidisciplinary effort to characterize the microbial diversity of our planet.

Author of more than 180 peer-reviewed journal articles and book chapters on microbial (met)a_genomics and approaches to ecosystem ecology, Gilbert currently serves on the advisory board of the Genomic Standards Consortium, and, until 1 July served as section editor for *PLOS ONE* and senior editor for the *ISME Journal* and *Environmental Microbiology*.

All articles from *mSphere™* and *mSystems™* will be open-access: immediately and freely available to ensure wide dissemination of research without paywalls. In addition, Creative Commons licensing assures copyright will always remain with the author.
The Rockefeller University—
a Milestone in Microbiology

The Rockefeller University was officially named a "Milestones in Microbiology" site by ASM in a ceremony at Rockefeller University on 8 April 2015, during which ASM Past President Stanley Maloy presented a commemorative plaque to Rockefeller President Marc Tessier-Lavigne. The Milestones designation recognizes the many groundbreaking achievements by Rockefeller scientists, with particular emphasis on Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty’s 1944 discovery that DNA from one pneumococcal type can transform cells of a different type, a finding that pointed to DNA as the molecule of heredity; Peyton Rous’ 1910 discovery that a virus in a chicken sarcoma could cause the same tumor type in inoculated healthy animals (his theory that viruses could cause cancer was proven correct, though nearly a half century after he proposed it); and Emil C. Gottschlich’s development of purified capsular polysaccharide vaccines against groups C and A meningococcal bacteria, which have prevented meningitis in infants, children, and American military recruits since 1970.

Milestones in Microbiology, a program of the Center for the History of Microbiology/ASM Archives (CHOMA), recognizes and honors institutions and scientists that have made significant contributions toward advancing the science of microbiology. For more information on the Milestones program, visit www.asm.org/milestones-in-microbiology

Reflections on Rockefeller University Contributions to Microbiology—Yesterday, Today, and Tomorrow

When the Rockefeller Institute for Medical Research was founded in 1901, infectious diseases were the most serious threat to human health—typhoid fever, tuberculosis, and diphtheria killed many people around the world, primarily poorer people but not sparing the affluent. In fact, the death of John Rockefeller’s grandson of scarlet fever that year is said to have been the stimulus for the creation of the Rockefeller Institute.

Louis Pasteur and Robert Koch had laid the groundwork for identifying microbes that cause specific diseases, and vaccines that could protect against infectious disease. It was clear that microbiology held the key to a healthier future and longer lives.

To thwart the threat of infectious disease, the Rockefeller Institute built a strong research program focused on understanding how bacteria, viruses, and parasites cause disease, and on how understanding the immune system could help in the development of new vaccines against these diseases.

Scientists at the Rockefeller made numerous achievements in microbiology, and I can only mention a few.

- Early in the 20th century, the Oswald T. Avery laboratory began studying Streptococcus pneumoniae (pneumococcus) infections. Scientists in his group showed that the outer capsule was a polysaccharide that conferred immunity to Streptococcus pneumoniae in mice, a discovery that later led to a vaccine in humans.
- As they continued to study how bacteria inherited the capsular polysaccharide, in 1944 Avery, Colin MacLeod, and Maclyn McCarty reported that DNA from one pneumococcal type could transform cells of a different type—demonstrating that DNA is responsible for heredity.
- In 1910, Peyton Rous found a virus in a chicken sarcoma that caused the same type of tumor in healthy animals inoculated with the virus—a discovery that took over 50 years to gain widespread acceptance. Over many subsequent decades, an understanding of how vi-
ruses can cause cancer was developed through the contributions of many individuals, including other Rockefeller scientists who conducted key studies. Rous shared the 1966 Nobel Prize for his seminal discovery.

- Later, Richard Shope showed that papilloma virus can cause cancer in mammals, providing the first evidence that viruses may also cause cancer in humans.
- Emil Gotschlich developed capsular polysaccharide vaccines that protect against Neisseria meningitidis. Since 1970, these vaccines have prevented meningitis in infants, children, and American military recruits, and reduced the impact of epidemics worldwide.

But we could recognize many other important discoveries as well, including:

- Hideyo Noguchi’s (1913) discovery of Treponema pallidum in the brain tissue of patients who had died of tabes dorsalis and general paresis, establishing that these neurological diseases are a late stage of syphilis.
- Thomas Milton Rivers’ (1920–1940) recognition that viruses are “obligate parasites” that depend upon living tissue for their growth and reproduction, leading to a tissue culture for vaccinia virus that served as the basis for the development of an anti-yellow fever vaccine.
- René Dubos brought an ecological approach to microbiology in his pioneering work on antibiotics, acquired immunity, tuberculosis, and bacteria indigenous to the gastrointestinal tract (now known as the microbiome).
- Thomas Francis Jr.’s isolation of the influenza A (1934) and influenza B (1940) viruses and development of an influenza vaccine.
- Gerald M. Edelman’s insights into the chemical structure of antibodies (coreipient of the Nobel Prize in Physiology or Medicine in 1972).
- Fritz Lipmann’s discovery of coenzyme A and its importance for intermediary metabolism (recipient of the Nobel Prize in Physiology or Medicine in 1953).
- Karl Landsteiner’s discovery of human blood groups (recipient of the Nobel Prize in Physiology or Medicine in 1930).
- Norton Zinder’s discovery of RNA phages.

These impressive accomplishments helped fulfill the hope for longer, healthier lives by reducing infectious diseases, although this is a battle that we will never stop fighting.

The Rockefeller did not only make impressive achievements in microbiology. The basic research at the institute also made many key discoveries in genetics, molecular biology, cell biology, developmental biology, and other areas that have shaped modern biology. And the impact of the Rockefeller went way beyond research in its own laboratories—the Institute served as an intellectual hub for scientists from around the world, who often made a stop at the Rockefeller when traveling to the United States from abroad to discuss the latest scientific discoveries. The impact continues to this day.


Stanley Maloy
San Diego State University
Past President of ASM

**Rockefeller University’s Role in the Development of the First Vaccines Against Meningococcal Meningitis**

Shortly after laboratories opened at the newly founded Rockefeller Institute for Medical Research in New York City, meningococcal meningitis spread through the city. About 4,000 cases of this disease, which frequently killed or severely disabled its victims, were documented in 1904 and 1905. At the time, these grim numbers were nothing extraordinary, as periodic outbreaks of diphtheria, smallpox, and other infectious diseases rippled through New York and elsewhere around the world.

But change was coming. Building upon earlier discoveries in microbiology, research at the Institute, now called Rockefeller University, would
make numerous contributions to a major shift: No longer would infectious diseases be the biggest threat to human health, at least in the developed world.

For its role in this transformation, Rockefeller University was named a “Milestones in Microbiology” site by ASM. “Today’s ASM Milestones in Microbiology recognition is a wonderful confirmation from our peers of the significance of the contributions Rockefeller scientists have made to the field of microbiology since our founding in 1901,” Rockefeller President Marc Tessier-Lavigne commented at the Milestones ceremony. “Microbiology was the cornerstone of Rockefeller’s mission at our founding, and it remains a vibrant field of study in our laboratories, along with its sister fields.”

Included in the recognized Milestone achievements was the development of the first vaccines against meningococcal meningitis—a key accomplishment that has protected people worldwide, and helped to turn this once-epidemic disease into a rarity in the United States. Among the Rockefeller faculty who attended the Milestones ceremony was Emil Gotschlich, the scientist who developed these vaccines. His name and accomplishments are cited on the Milestones plaque.

**Meningitis, Then and Now.** During the 1904–05 epidemic, meningitis killed 73.5% of those it infected, a typical mortality rate for the disease during the first half of the 20th century. Caused by infection with the bacterium *Neisseria meningitidis*, meningococcal meningitis has symptoms—fever and chills, confusion, nausea and vomiting, headache and stiff neck—that can resemble those of less-serious illnesses. However, the infection causes potentially damaging or fatal inflammation in the lining of the brain and spinal cord. Those who survive the infection often suffer hearing loss, cognitive problems, and seizure disorders, or must have limbs amputated because of damage to blood vessels. Viruses, fungi, and a number of species of bacteria can cause meningitis, with *N. meningitidis* being one of the most common bacterial culprits.

More than a century later, vaccines target the most prominent meningitis-causing strains of bacteria, and infections can be treated, although not always successfully, with antibiotics. These measures have largely relegated bacterial meningitis to headlines describing distant outbreaks, such as the recent one in Nigeria, or the sudden, often isolated deaths it causes in the United States. Gotschlich’s work helped usher in this new paradigm for meningitis, changing it from a familiar killer to a rare and distant threat.

**Antibodies and Antiserum.** As is almost always the case with scientific achievements, the first meningococcal vaccines built on numerous earlier discoveries. In his remarks at the ceremony, Gotschlich began his story with a fundamental discovery about how the body protects itself against invaders with a substance in blood, later called antibodies.

In 1890, Emil von Behring and Kitasato Shibasaburo, working in Robert Koch’s lab in Germany, discovered that the blood of animals immune to diphtheria and tetanus could not only neutralize their toxins but could also cure when transfused to other infected animals. This discovery led to the development of antiserum, also called antitoxin at the time, a clear liquid derived from the blood of infected horses with the blood cells and clotting factors removed. This approach was applied to a number of infectious diseases, including meningitis caused by the bacterium *Neisseria meningitides*.

The meningitis antiserum was originally injected under the skin, an ineffective way to deliver it, because the infection wreaks neurological havoc after passing through the blood-brain barrier. In experiments following the 1904–05 epidemic, Simon Flexner, founding Director of the recently established Rockefeller Institute, found injecting the antiserum directly into the spinal column served as a better treatment—reducing mortality by more than half. However, the antiserum was difficult to produce, and its effects were unpredictable.

Work on another deadly bacterium, pneumococcus, the cause of a range of infections including pneumonia and meningitis, provided the next major step forward. In the 1920s, Michael Heidelberger and Oswald T. Avery at Rockefeller uncovered the precise chemical features of the bacteria that provoke a specific immune response. The capsule around the bacterial cells triggered the response, which varied depending on the type of pneumococci. While all immune substances were at the time thought to be proteins or derivatives of them, Heidelberger and Avery showed the capsule was composed of polysaccharide, or carbohydrates containing a number of sugar molecules. Their discoveries led to work on vaccines against pneumococci, meningococci, and other infectious organisms, using specific polysaccharides to induce the production of antibodies against the specific bacteria. Then,
in 1945, “disaster” arrived in the form of penicillin and other antibiotics, Gotschlich said. With these new treatments for infections, interest in vaccines disappeared.

**A Vaccine Revisited.** Meningitis was a longstanding problem for the military during any large mobilization, and for a time, new sulfa antibiotics kept a lid on outbreaks by ridding carriers of the microbes. But, as history has since shown, bacteria will find ways to thwart antibiotics given time, and the escalation of the war in Vietnam in 1964 coincided with the rise of sulfateresistant meningitis microbes.

The following year, Gotschlich, then a scientist at Rockefeller studying the polysaccharides within the pneumococcal capsule, received a promotion to Assistant Professor and was subsequently drafted. Upon entering the Army, he was assigned to work for a special meningitis-focused section within the Walter Reed Army Institute of Research.

Meningitis vaccines had been attempted years earlier using capsule polysaccharides, but they failed to effectively stimulate an immune response that would provide future protection against the microbes. Gotschlich decided to re-examine the purification and chemistry of the capsule polysaccharides, suspecting that these complex molecules were deteriorating during the process used to make the vaccine. Working with Irving Goldschneider, Teh Yung Liu, and Malcolm S. Artenstein, Gotschlich developed a new technique to effectively isolate polysaccharides from two types of *N. meningitidis*, A and C.

Initial tests failed to bring about an immune response in a number of animals. “It was well known humans responded better to purified polysaccharides than animals and, in November of 1967, I inoculated myself,” Gotschlich said. By the end of the year, his blood work made it clear that both A and C polysaccharides were immunogenic.

A small trial with five additional volunteers followed, and, later, larger-scale military trials showed the group C vaccine to be 90% effective at provoking an adequate immune response and eradicating the microbes from a large portion of carriers. Because group A is rare in the United States, the development of the vaccine against it happened elsewhere in the world.

**A New Reality.** Since their creation, group A and C vaccines have been administered to billions of people, including all Chinese children since 1984, Africans facing seasonal epidemics in the sub-Saharan meningitis belt, and pilgrims making the holy journey to Mecca in Saudi Arabia. Over time, new and modified meningitis vaccines have continued to fill in the gaps. For example, polysaccharide vaccines were not always effective for very young children, so researchers developed conjugate vaccines that linked a capsule polysaccharide to another immune-stimulating protein, a strategy that also had its roots in immunological work conducted decades earlier at Rockefeller. This approach led to a dramatic decline in cases of meningitis caused by *Haemophilus influenzae* type b in the United States, which can kill infants and young children or leave them deaf, blind, or cognitively impaired.

Taken together, the development of the *Haemophilus* and meningococcal vaccines represents a major advance in public health, one achieved by groups of scientists working together for decades, according to Gotschlich.

As a result of the development of these vaccines, the landscape for meningitis has changed dramatically in the United States. Instead of epidemic waves affecting thousands in a single city, only 800 to 1,500 Americans contract meningococcal meningitis annually, according to the U.S. Centers for Disease Control and Prevention. The primary cause of these infections, group B meningococci, has been a recalcitrant target for vaccines, because its capsule mimics sialic acid-containing molecules in the human body. But recently, vaccines that target group B surface proteins, rather than its capsule, have been introduced.

Gotschlich sees the introduction of MenAfVac, a low-cost conjugate vaccine against group A developed specifically for use in Africa’s meningitis belt, as an outstanding success. However, there remains a need for an affordable conjugate vaccine covering other groups as well, he said.

For more information on Rockefeller University, see www.rockefeller.edu.

** Wynne Parry  
Staff Writer, Rockefeller University**
ASM Public Affairs

Federal Funding Opportunities Breakfast at asm2015

During asm2015 in New Orleans, the Public and Scientific Affairs Board (PSAB) sponsored the Federal Funding Opportunities Breakfast, which allowed attendees to learn about funding opportunities available to microbiologists from several federal agencies that support biomedical, environmental, and life sciences research. Presenting at the breakfast were Shiva P. Singh, Ph.D., Chief, Undergraduate and Predoctoral Training, National Institute of General Medical Sciences National Institutes of Health; Elizabeth R. Blood, Ph.D., NEON Program Director, National Science Foundation; and Joseph R. Graber, Ph.D., Program Manager, Team Lead for Genomic Science, Biological Systems Science Division, Office of Biological & Environmental Research, U.S. Department of Energy. The presentations from the breakfast are available on the Public Affairs website at http://www.asm.org/policy.

ASM Participates in White House Antibiotic Stewardship Forum

Over 150 stakeholders in human and animal health met on 2 June at the Antibiotic Stewardship Forum at the White House to highlight commitments to implement changes over the next five years to slow the emergence of resistant bacteria and prevent the spread of resistant infections. Gail Cassell, Chair of the ASM Public and Scientific Affairs Board Committee on Biomedical Research, represented ASM at the White House Forum. More information, including fact sheets on the Forum and the Center for Disease Control and Prevention’s AR preservation efforts, is available at http://bit.ly/1KQhPaJ.

DoD Alert on Recent Inadvertent Shipment of Anthrax to Laboratories

The Department of Defense (DoD), Nuclear Chemical and Biological Defense Programs, Chemical and Biological Defense and Threat Reduction Program Oversight Offices requested ASM send a statement to members regarding the inadvertent Shipment of Live Bacillus anthracis (anthrax) to laboratories in the United States and overseas. The bulk e-mail was sent out in early June. The statement is available at http://www.asm.org/index.php/public-policy/93-policy/93545-dod-6-4-15.

ASM Provides IQCP Materials for Clinical Microbiology Lab Personnel

The Centers for Medicare & Medicaid Services (CMS) are implementing an Individualized Quality Control Plan (IQCP) as a new quality control option based on risk management for CLIA laboratories performing non-waived testing. This plan, begun in 2012, becomes effective January 2016. Beginning with a sponsored conference call with CMS during asm2014, a special interest session at asm2015, and in a joint project with the College of American Pathologists (CAP) and the Clinical and Laboratory Standards Institute (CLSI), ASM is helping clinical microbiologists prepare for implementation of IQCP in their laboratories. You can find the relevant IQCP templates, forms, asm2015 presentations, and CMS instructions by going to http://clinical.asm.org/index.php/lab-management/laboratory-management/445-iqcp-iqcp.

NIH Office of Science Policy Announces the Launch of a New Blog

The National Institutes of Health launched a new Office of Science Policy (OSP) blog “Under the Poliscope: Bringing Science Policy Into Focus,” which will highlight the activities of the NIH Office of Science Policy and focus on science policy matters in general as well as emerging issues of interest to the life sciences community and public at large. NIH encourages readers to provide their thoughts and ideas to stimulate a dialogue between NIH and its stakeholders. To subscribe to “Under the Poliscope,” go to http://osp.od.nih.gov/under-the-poliscope.

ASM Selects Congressional Science Fellow for 2015–2016

ASM has awarded the ASM Congressional Science Fellowship to David K. Visi for 2015–2016. David will work on the staff of a member of Congress or congressional committee during his fellowship year.

David earned his Ph.D. in Molecular Biology and Biochemistry at the University of North Texas in the Spring of 2013 working in the lab of Michael S. Allen. His doctorate focused on the microbial constituents in the retting of Hibiscus cannabinus for incorporation into a green biocomposite, which included utilizing next-generation sequencing of 16S genes as well as establishing the initial computational pipeline. Recently, he was the 2015 Christine Mirzayan Science and Technology Policy Fellow at the National...
ASM has supported Congressional Fellows since 1977. The ASM Congressional Science Fellowship Selection Committee selects a postdoctoral to mid-career microbiologist to spend one year on the staff of an individual congressman, congressional committee, or with some other appropriate organizational unit of Congress. Prospective Fellows must be citizens of the United States and members of ASM for at least one year and must have completed their Ph.D. by the time the fellowship begins in September. The Congressional Science Fellowship is supported in part by the Frobisher Fund, a bequest made to ASM by Martha L. Frobisher.

The ASM General Meeting Minority Travel Award program offers travel funds to increase the participation of underrepresented minority (URM) groups in the ASM General Meeting. The following outstanding 2015 awardees were introduced at the ASM General Meeting:

Thessicar E. Antoine, Ph.D., Georgia State University, Viral Immunology Center
Filipa Godoy-Vitorino, Ph.D., Inter American University of Puerto Rico, Metropolitan Campus

Camille A. Hardiman, Ph.D., National Institutes of Health
Laurice J. Jackson, Tufts University
Abria Magee, Ph.D., Baylor College of Medicine
Lindsey L. O’Neal, University of Oklahoma, Department of Microbiology
Ashley S. Parker, Ph.D., National Institutes of Health, National Cancer Institute
Nina M. Poole, Ph.D., Baylor College of Medicine

To promote awareness of the diversity of careers available in the microbial sciences, nearly 40 microbiologists volunteered during the Board’s fourth an-

Education Board

Education Board Activities at asm2015

During each General Meeting of the Society, the ASM Education Board sponsors several professional development events for members. At asm2015 in New Orleans, the following Board activities helped deepen the meeting experience for conference attendees.

For students, the Board sponsored the 4th annual ASM Research Capstone Institute. Designed to prepare students to attend and present at professional meetings, the institute was held on 29–30 May. Its 62 participants—all Board fellow and awardee presenters at asm2015—received an orientation to the conference, a forum to practice their research presentations, and professional development in the form of sessions on poster etiquette, elevator talks, networking, career planning, and more. A continual highlight of the institute is the peer mentoring and testimonies that ASM Robert D. Watkins Graduate Fellows provide to the institute’s undergraduate participants.

For ASM members, the Board sponsored the ASM General Meeting Minority Mixer. The reception was hosted by the Chair of the Committee on Microbiological Issues Impacting Minorities (CMIIM), Dwayne Boucaud. The reception was attended by members of the committee and the leadership of ASM, including ASM President Tim Donohue.

The grants are supported by the American Society for Microbiology. For more information go to the ASM website: http://www.asm.org/asmm minoritytravelgrant.
annual career session, Microbiology Career Choices: What’s Available and How to Succeed. The session, an asm2015 preconference workshop for about 500 student and postdoctoral fellow participants, took place on 30 May. As career “advisors,” the volunteers offered insight on a wide range of careers by sharing glimpses into their work—responsibilities, expectations, salary, getting started, and advancement—in roundtable discussions with 10 to 12 participants. Advisers represented industry, clinical labs, government agencies and labs, nonprofits, undergraduate teaching institutions, and doctoral universities/professional schools.

To advance the ASM member challenge “Every Member a Mentor,” the Board led a two-part mentoring workshop on 30 May. The first part, Mentor Training for Microbiologists, featured accelerated mentor training designed to foster success among research mentors of undergraduates, graduate students, postdoctoral trainees, and faculty. There were 44 attendees for this portion of the training, which was developed from “Entering Mentoring,” an evidence-based mentor-training curriculum of case studies and facilitated discussions. The second part, Facilitator Training for Research Mentors, was a special train-the-trainer experience that drew 46 attendees. Participants learned ways to develop the knowledge and skills to implement mentor training, gain confidence in their facilitation skills, describe evidence supporting the effectiveness of research mentor training, and more. The workshop was sponsored by the ASM-NSF Leaders Inspiring Networks and Knowledge (LINK) Program, an initiative of the ASM Education Board and NSF Directorate for Biological Sciences (NSF grant #1241970).

On 30 May, the Board offered The Business of Science: Leveraging Your Ph.D. to Successfully Transition from Student to Professional, a preconference session targeted to graduate students, postdoctoral fellows, and early-career scientists. The session drew about 86 attendees and presented ways that mastering scientific, business and social skills can lead to success as a scientist in both industry and academic settings. Topics included 24 competencies identified as critical in being competitive and successful in industry, and how the competencies relate to the graduate and post-graduate education experiences of scientists.

For graduate students and postdoctoral fellows, the Board offered the asm2015 special interest session Using an IDP to Plan a Successful Scientific Career on 1 June. Eighty participants attended the session, which offered an introduction to individual development plans (IDPs) and how the plans can contribute to achieving research and career goals. Session topics included IDP components; sample plans; ways that research, individuals, institutions, and mentors can use IDPs; and resources for creating the plans.

In 2016, the Society will debut ASM Microbe, which integrates ASM’s two most popular events—the General Meeting and ICAAC—into one meeting. Set for 16–20 June in Boston, Mass., the meeting will feature a dynamic Education Board lineup. Stay tuned to www.asmmicrobe.org for details.

ASM Represented at National Student and Educator Meetings

The strategic directions of the ASM Education Board include collaborating with national organizations to promote microbiology education at all levels. In spring 2015, the Board sponsored the Society’s participation in several events focused on science students and educators.

National Conference on Undergraduate Research. Education staff member Irene Hulede represented ASM at the National Conference on Undergraduate Research (NCUR), held 16–18 April in Spokane, Wash. The mission of NCUR is to promote undergraduate research scholarship and creative activity done in partnership with faculty or other mentors as a vital component of higher education. The national conference is an interdisciplinary event where students representing universities and colleges from across the United States and around the world make oral and poster presentations.

Fellowship Roundtable. Education staff members Amy Chang, Irene Hulede, and Tiffani Fonseca represented ASM at the Fellowship Roundtable held at the Keck Center of the National Academies on 30 April. The Roundtable meets bi-annually in Washington, D.C., to discuss fellowship administration and best practices and to share information and concerns about individual fellowship programs. This meeting marked the Roundtable’s 20th anniversary.

Future of Bioscience Graduate and Postdoctoral Training. Education Director Amy Chang and Committee on Graduate and Postdoctoral Education Chair Cynthia Cornelissen represented ASM at the Future of Bioscience Graduate and Postdoctoral Training, a national meeting at the University of Michigan (Ann Arbor) on 3–5 May. Attendees included academic institutions, funding agencies, scientific societies and others interested in discussing strategies to prepare students for biomedical careers in a future where an estimated 80% of these careers will be outside of academic research. Workshops at the meeting analyzed existing ideas for change, new training models, and possible policy recommendations that could promote fundamental changes in how bioscientists are educated in the United States.

Understanding Interventions that Broaden Participation in Research Careers. Irene Hulede represented the Society at the 7th Annual Conference on Understanding Interventions that Broaden Participation in Research Careers, held 15–17 May in San Diego, Calif. The goal of the meeting was to
facilitate the dissemination and exchange of hypothesis-based research on interventions and initiatives that broaden participation in science, technology, engineering, and mathematics (STEM) research careers. Attending were behavioral/social science and education researchers, evaluators, faculty, and graduate students in STEM fields who participate in interventions programs.

**ASM Scientific Writing and Publishing Institute: Program Impacts and Expansion**

To support beginning scientists in advancing academically and professionally in the microbial sciences, the Society has offered its ASM Scientific Writing and Publishing Institute (SWPI) since 2010. Sponsored by the ASM Committee on Graduate and Postdoctoral Education, the SWPI is led by ASM members who have published widely, reviewed manuscripts, and served on the editorial boards of major journals. In 2015, the Committee conducted a comprehensive survey to measure the effectiveness, strengths, and weaknesses of the institute; gather information on the achievements of its alumni; and highlight opportunities to strengthen the program.

**Comprehensive Survey.** Of the 93 graduate students and postdoctoral fellows who attended the institute between 2010 and 2014 (five cohorts), 56 (60%) took part in the survey. About 45% of respondents were postdoctoral scientists, and 17.8% were graduate students; 19.6% were employed in the microbial sciences, and 16.1% were employed outside the microbial sciences. Only one respondent was unemployed. Among the survey results (available at http://www.asmgap.org), key findings include the following:

- Twenty-three have published manuscripts in ASM journals, including 12 as first authors.
- On a scale of 1 (strongly disagree) to 5 (strongly agree), the majority said that after attending the institute they had a greater understanding of preparing a manuscript (89.3%; average rating, 4.16), submitting a manuscript (78.6%; average rating, 3.89), and the writing and publishing process (83.9%; average rating, 4.14).
- Five (8.9%) have kept in touch with a facilitator and 13 (23.2%) with a participant from the institute.
- About 95% said they had recommended the institute to one to five colleagues.

**Program Expansion.** A second Committee effort was expanding the program to a two-part training initiative containing several introductory webinars and a multiday, in-person workshop. The 2015 webinars and workshop, known as SWPI Online and SWPI Face-to-Face, respectively, emphasized useful tips and hands-on practice for understanding the scientific writing, publishing, and review processes:

**SWPI Online.** The inaugural SWPI Online took place as four-part webinar series in January through March 2015. About 70 graduate students, postdoctoral fellows, and early-career scientists attended, and topics included overviews of journal publishing, writing scientific papers, and scientific publishing ethics. The series also included pre- and post-webinar assignments, structured mentoring, and a community of practice. Online events were broadcast live, and participants had numerous opportunities to submit questions as they listened in with their peers.

**SWPI Face-to-Face.** The face-to-face institute took place in Washington, D.C., on 19–22 March 2015. Eight senior-level graduate students and two postdoctoral fellows attended, and all were immersed into the essentials of scientific writing and publishing. Emphasis was placed on substantial time for participants to benefit from one-on-one feedback from facilitators, writing practice, and stimulating discussions and interactions. Before the institute, all participants submitted manuscripts for pre-SWPI assessment, and after the institute, they left with detailed plans for improving their manuscripts, tools and resources for developing future publications, and a network of peers and mentors for critiques and advice.

**Looking Ahead.** Plans for the 2016 program are under way: SWPI Online will be held in January-March and expand to six webinars focused on didactic components of scientific writing and publishing. SWPI Face-to-Face will take place in the summer and focus on intensive writing and one-on-one consultations. Participation in both programs is beneficial for attendees, but not required. Learn more at http://www.asmgap.org.

ASM offers the SWPI with partial support from the Burroughs Wellcome Fund.
bacteriology, parasitology, virology and host immunity. (For more details see Microbe, September 2014, p. 380.) The well-attended 44th Annual Symposium, entitled Current Advances in Clinical Microbiology, featured six presentations covering a variety of topics related to Clinical Microbiology and cutting edge technology. Once again, the Symposium Committee assembled an eclectic faculty to stimulate ideas and discussion on recent developments in Clinical Microbiology. The symposium included two major topic areas: Section I—Advances in the Detection of Bacterial Pathogens and of Antimicrobial Resistance; Section II—Advanced in the Detection of Viral Pathogens.

It should be noted that prior to routine meetings, the Branch Executive Committee meets to bring various Branch Committees together to keep the momentum of the Branch moving forward. Also, the Branch website (http://www.epaasm.org/) continues to grow to serve the needs of members and to encourage new microbiologists to become active in the Branch.

ASM Tri-Branch Meeting

This Spring 124 current and future microbiologists from the Rio Grande, Intermountain and Rocky Mountain ASM Branches met at Fort Lewis College in Durango, Colo. ASM Distinguished Lecturers included Dr. John Stolz from Duquesne University who described bacterial life in the frac pit and Dr. Jill Stewart from University of North Carolina who presented evidence for global environmental changes especially addressing the question “Are we making populations of antibiotic resistant bacteria?” Dr. Steve Hamner represented our host College with the keynote lecture describing water quality and public health risks posed by bacterial pollution in rivers in India and Montana. The meeting began Friday (April 24, 2015) evening and closed Sat. evening during which time 24 talks and 42 posters were presented. Senior faculty volunteered to judge the presentations and awarded 14 prizes to outstanding undergraduate, graduate and postdoctoral presenters. Drs. John Meyers and Terry Ann Else represented National ASM whose generous support provided 61 student travel awards. By all measures, the meeting was a successful event that united microbiologists from the Rio Grande, Idaho, Nevada, New Mexico, Texas, Utah and Wyoming and provided the platform for future collaborations between our three Branches.

Betsy Kleba
President, Intermountain Branch

Kathryn Hanley
President, Rio Grande Branch

Dan Wall
President, Rocky Mountain Branch

The Eastern Pennsylvania Branch 2014 Activities. In 2014 the Eastern Pennsylvania Branch held seven Monday evening meetings consisting of a one hour food and discussion reception, followed by a formal presentation, with time allocated for questions and discussion after the presentations. The following topics were presented: chemokine receptor targeting of Staphylococcus aureus; combatting antibiotic resistance; problem based learning; importance of the History of Microbiology; aspects of virology and oncology in varied settings; Listeria monocytogenes, a topic featured at two meetings, one focusing on its pathogenic transition and one on its mechanisms of intracellular survival. The December meeting was preceded by several graduate student presentations, organized by the Branch Student Chapter. Meetings were held on the University of Pennsylvania campus, except for a special meeting held at Thomas Jefferson University to commemorate the official transfer of the Branch Archive Collection to Thomas Jefferson University to be part of their Archive Collection housed at the Scott Memorial Library. It is hoped that this event will inspire other Branches to consider organizing their historical material and seek out a university or medical school library to showcase the material.

In addition to the regular scheduled meetings and archive event, the Branch held the 23rd Annual Philadelphia Infection and Immunity Forum in May and the 44th Annual Symposium in November. The Infection and Immunity Forum, mainly organized by the Branch Student Chapter, included a full-day meeting bringing together 103 participants with three invited speakers, and six graduate and postdoc speakers. It also included 42 poster presenters demonstrating research related to bacteriology, parasitology, virology and host immunity. (For more details see Microbe, September 2014, p. 380.) The well-attended 44th Annual Symposium, entitled Current Advances in Clinical Microbiology, featured six presentations covering a variety of topics related to Clinical Microbiology and cutting edge technology. Once again, the Symposium Committee assembled an eclectic faculty to stimulate ideas and discussion on recent developments in Clinical Microbiology. The symposium included two major topic areas: Section I—Advances in the Detection of Bacterial Pathogens and of Antimicrobial Resistance; Section II—Advanced in the Detection of Viral Pathogens.

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Mike Schmidt
Chair, Branch Organization Committee

ASM NEWS
Microbe Mentor

How do I prepare myself for a position in microbiology with a different focus than what I was trained in? For example, I would like to do work in industry, but my thesis work has been in very basic research.

The short answer is: talent is a currency accepted everywhere, and an educated and well-rounded microbiologist is a valuable commodity no matter what the work sector. To elaborate on this idea, the Microbe Mentor reached out to Paul Dunman, Associate Professor of Microbiology and Immunology at the University of Rochester School of Medicine and Dentistry, who replied:

A common misconception is that trainees with purely basic research experience do not have the proper skill-set and are not qualified for industrial positions. That could not be farther from the truth, particularly if one considers that virtually every industrial project is predicated by a basic understanding of the system of interest. For instance, members of “translational” research teams are actually conducting basic studies on a daily basis, whether it’s validating a particular target, defining the kinetics of an enzyme, designing an assay, or problem solving a reagent issue. Success in each of these examples requires basic research skills to quickly devise an appropriate experimental plan.

The challenge for basic scientists in transitioning to the private sector is finding job opportunities. Most basic researchers probably do not attend the same meetings frequented by industrial scientists, or collaborate with private groups. Consequently, they lack the connections needed to learn about jobs available in big-pharma or biotechnology companies. It may be possible to find an advisor or Departmental member with industry ties to get you started, but like any job search the simple truth is that one must be aggressive, original, and persistent.

To that end, begin the search very early. Make business cards and attend meetings that you know industry personnel frequent. Strike up conversations, hand out those cards, and let people know you will be on the job market.

Publish your work in a timely manner: publications are collateral, and the number/impact of your publications does matter. One Antimicrobial Biotechnology Chief Scientific Officer uses an applicant’s publication record as the strongest predictor of productivity, and therefore won’t consider one who doesn’t have at least three authorships. Read the literature and, if appropriate, follow up with the corresponding author of studies published by companies. Consider internships for Ph.D.-level trainees. Also, most of the sales representatives that you may interact with (or try to avoid) sell to companies, have contacts within those companies, and may be helpful in your search.

Once you get that interview, be prepared to be judged on your science as well as your presentation skills—the ability to describe your hypothesis, experimental plan, and delivery, and to answer questions. Much of industrial life is scientific presentations and you will be asked to provide a formal seminar on your work. Since you will likely meet one-on-one with other team members during the interview day, be sure to have read their past work so you can drive the conversation and convey your thoughts about the work. Most likely, you will not have signed a Confidential Disclosure Agreement (CDA), so your interviewer can’t tell you about their current project—but pivoting the conversation to their past work offers you the opportunity to engage in a productive dialog where you can share your thoughts. While you will certainly be nervous during the interviewing process, enjoy yourself. One of the main goals of any company hire is to ensure that they are investing in a bright talent who will fit well with the team.

Big pharma and biotechnology companies are most interested in building scientific teams comprised of energetic, productive, innovative, and well-trained personnel that work well in a collaborative manner. Young scientists who display the ability to think through a problem and engineer a highly focused and well-controlled experimental plan to test their hypotheses are the most highly
sought after. At the end of the day, industrial jobs are available (and you are qualified), but just as in science, you must carefully research what opportunities exist and carefully plan how to obtain the results you seek.

Paul Dunman
Paul Dunman is currently an Associate Professor of Microbiology and Immunology at the University of Rochester School of Medicine and Dentistry. He received his Ph.D. from the Department of Microbiology and Immunology at the University of Medicine and Dentistry of New Jersey in 1999 and subsequently obtained postdoctoral training then as a Scientist and Senior Scientist positions in the antibacterial and bacterial vaccines groups at Wyeth Pharmaceuticals. Dr. Dunman transitioned to a faculty appointment at University of Nebraska Medical Center prior to joining the University of Rochester in 2010. His laboratory research focus is to validate targets and strategies for the therapeutic intervention of bacterial infections.

Want to know more about Microbe Mentor and ASM career offerings? Sign up for the monthly notification list at microbementor@asmusa.org. Each message will include a sneak peek at the upcoming column, career and mentoring news, and more!
Reviews and Resources

BOOK

The Vital Question: Energy, Evolution and the Origins of Complex Life
Nick Lane. W.W. Norton, New York, 2015, 305 p., $27.95.

If I were a rich man, I would buy up the print run of this book and give a copy to every science undergraduate ahead of his or her first course in cell biology. It would serve nicely as an antidote to the standard textbooks, crammed to the gills with chewy factual detail, that have grown too heavy to carry, let alone read. Surely, what draws students into science is not an overmastering desire to add another pebble to that gigantic pile, but the prospect of touching the mystery of life and perhaps making a contribution to understanding the universe!

The Big Questions—that’s what Nick Lane’s book is about. Why is life the way it is? Why do we have prokaryotes and eukaryotes, but no intermediate forms? Why do all living things harvest energy by means of ion currents, despite the awkward complexities of that mechanism? Why is sex ubiquitous among eukaryotes? Could matters have been otherwise, or were life’s solutions constrained by its physical framework? There are many basic questions yet to be answered, but Lane rightly singles out two topics as central: the origin of life, and the origin of the eukaryotic cell. He writes elegantly and with infectious passion, in a vigorous conversational style accessible to the general reader. But he also has serious points to make, and demands attentive reading.

It is not Lane’s purpose to present a conventional, consensus treatment; he is making an argument, and his views are very much his own. The origin of life is most commonly presented in terms of the primacy of information: a self-replicating macromolecule arose spontaneously in the primordial broth, and all else followed. Lane rejects this scenario (as do I), and underscores the role of energy as the indispensable driving force.

He is one of a small but growing school of thought that favors submarine hydrothermal vents as the most plausible venue for genesis, enabled by the supply of geothermal energy and raw materials so structured as to prefigure chemiosmotic energy conversion. Ion currents are universal because they were part and parcel of life from its inception, long antedating genes. Energy also enters into the origin of the eukaryotic cell, which Lane attributes to the endosymbiotic association of an archaeal cell with a proteobacterium that became the mitochondrion. Mitochondria came very early, and were indispensable to the rise of eukaryotic complexity. The essential difference between prokaryotes and eukaryotes is that the latter command far more energy per gene, and the only way that can be achieved is by the domestication of endosymbionts.

The consequences ramify across the history of life, bearing upon such perennial favorites as ageing, death, and sex. Lane sees the origin of eukaryotic cells as an exceedingly rare event of transcendent significance in the history of life, possibly a unique one.

The origin and early evolution of cells are intensely controversial subjects, and Lane’s interpretations will not be shared by all of his colleagues; this reviewer questions several of the specifics. But that is exactly what makes this book so admirable: it exemplifies science as the continuing quest to make sense of the world. We meet here an individual, thoughtful, and exceedingly well-informed scholar grappling with some of the deepest questions in biology. This is what scientists are supposed to do, and whether or not one buys into the details one must applaud Lane’s bravery and respect his purpose.

Franklin M. Harold
Seattle, Wash.
Application Deadlines

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 24 and 31 August to be considered for UFRI’s Fellowships for the 2015 ASM Conference on Biofilms and the 2015 ASM-ESCMID Conference.

WWW: http://www.asmlink.org/ufri

Deadlines: 24 and 31 August 2015.

ABRCMS 2015: Accepting Abstracts and Travel Award Submissions

Exhibitor and attendee registration, abstract submissions, and travel award submissions are all open for the 2015 Annual Biomedical Research Conference for Minority Students (ABRCMS), set for 11-14 November in Seattle, Wash. This year marks the 15th anniversary for the conference, and attendees will benefit from a distinguished roster of speakers, along with numerous workshops, scientific presentations, professional development opportunities, networking events, and more. 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 scientist 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.

WWW: www.abrcms.org

Deadlines: 1 September, 11 September, and 25 September 2015 (see above).

ASM-IUSSTF INDO-US Professor in Microbiology

Sponsored by the Indo-US Science & Technology Forum and managed by ASM, this program offers two professorships with the intent to foster collaboration and scientific exchange between the United States and India. “Teaching Professorships” provide microbiologists in India and the United States with an opportunity to visit institutions in the other country to teach an interactive short course on a topic in any of the microbiological disciplines. “Research Professorships” provide support to microbiologist in India and the United States to conduct a novel research project in partnership with a colleague at a research facility in the other country. Applications should be submitted jointly by the prospective visiting professor and host.


Deadline: 15 December 2015.

National Registry of Certified Microbiologist (NRCM) Certification

Certification is offered in biological safety and quality; and pharmaceutical and medical device. NRCM certification is achieved by passing an online multiple-choice exam that is offered daily in the month of April at testing centers worldwide.

WWW: www.asm.org/nrcm

Deadline: 1 February 2016.

About Application Deadlines

The Application Deadlines section provides ASM members with information about certification programs, awards, and fellowships sponsored by ASM. More resources are available to members on the website at http://www.asm.org/index.php/awards-grants-whats-new-in-asm-awards-grants-fellowships-and-professorships.html. The website provides direct links to program Web pages for complete details, including eligibility requirements and application information.
ASM Meetings Calendar

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/

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.
Employment

POSITIONS AVAILABLE

Professor, Associate Professor, or Assistant Professor without Tenure

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Small Things Considered

Polintons—a Viral Missing Link?
http://schaechter.asmblog.org/schaechter/2015/03/polintonsa-viral-missing-link.html
by Jamie Henzy

The line between viruses and parasitic elements of the genome is thin and delicate, and probably often crossed. Parasitic elements that acquire the means to escape the host cell become viruses and, conversely, viruses can lose this ability and return to a more limited lifestyle as transposable elements (TEs). Add horizontal gene exchange to the mix, and you get a tangle of evolutionary relationships difficult to sort. Enter Polintons: large DNA transposons, typically 15 – 25 kb in length. Their wide distribution among eukaryotes—from fungi and trichomonads, to frogs, crocodiles, and insects—speaks to their ancient origins. Now Krupovic and Koonin demonstrate their central position in the evolution of a wide range of TEs and eukaryotic viruses.

Viral “hallmark” genes encode proteins for replication and the generation of virus particles. Shared among a wide range of viruses, they are useful for defining deep evolutionary relationships. Two such genes code for the major and minor capsid proteins that form an icosahedron around the genomes of many DNA viruses, protecting them during their infectious forays. Polintons not only possess capsid genes, attesting to their viral bona fides, but their major capsid gene is most closely related to that of a giant DNA virus of the proposed Megavirales order. Connecting Polintons to an altogether different type of virus—bacteriophages of the Tectiviridae family—are genes for an ATPase (for pumping the genome into the capsid) and a protein-primed replication enzyme (pPolB). These and other gene homologies relate Polintons to a remarkable variety of elements with different lifestyles and host ranges—cytoplasmic plasmids, bacteriophages, viruses, and virophages, whose hosts span archaea, bacteria, and eukaryotes.

The authors untangle these threads of homology to offer the following hypothesis for Polinton origins and their role in the evolution of multiple viruses/TEs. The bacterial endosymbiont that gave rise to the mitochondria of eukaryotic cells carried a primitive tectivirus—the Polinton ancestor. Through recombination with a DNA transposon, the “proto-Polinton” acquired genes for a cysteine protease and an integrase. The protease was adapted over time for its role in virus maturation, and retained in various viral lineages that emerged from Polintons, which include virophages, adenoviruses, and Megavirales. The integrase, which mediates insertion into the host genome, provided the ancestral Polinton with the option of a largely sedentary lifestyle within the host genome as opposed to a virus-like, freewheeling lifestyle. Integrase-bearing Polinton ancestors, for example, found great success in the sedentary lifestyle within the parasitic protozoan Trichomonas vaginalis, where they expanded to comprise ~30% of the genome and gave up capsid genes altogether. By contrast, Polinton ancestors of adenoviruses lost the integrase gene, kept the capsids genes, and took up a life of travel and adventure as viruses.

Polintons and adenoviruses both replicate in the nucleus. So in order to spawn the giant dsDNA viruses, which replicate in the cytoplasm, a Polinton ancestor first had to escape the nucleus. This bold move meant forfeiting reliance on the cellular polymerase for transcription. Ancestral Polintons succeeded in this by acquiring RNA polymerase (RNAP) and an mRNA-capping enzyme from the host, spawning the linear cytoplasmic plasmids of eukaryocytes. However, linear cytoplasmic plasmids replicate with pPolB, which primes from only one site (the 5’end)—this could be problematic for the longer genomes of Megavirales. The workaround? Primase-helicases enable the use of multiple internal primers, allowing longer genomes to be replicated. Megavirales encode primase-helicases that are homologous to those found in several Polintons, suggesting that acquisition of a Polinton primase-helicase allowed Megavirales to expand their genomes, adding genes left and right from various sources—bacterial and eukaryotic alike—and eventually reaching their gargantuan genome sizes.

So what do bacteriophages, virophages, linear cytoplasmic plasmids, and giant DNA viruses have in common? Polintons on their ancestral trees, of course! Thus the Polintons warrant the title Krupovic and Koonin bestow upon them: “a hotbed of virus evolution.”

Jamie is a postdoctoral researcher in the lab of Welkin Johnson at Boston College.

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