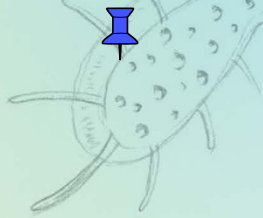
Elio Schaechter
Artwork by Judith Schaechter



In the Company of Microbes

Ten Years of Small Things Considered

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Ten Years of *Small Things Considered*

Washington, DC

Library of Congress Cataloging-in-Publication Data

Names: Schaechter, Moselio, editor. | Schaechter, Judith, 1961- illustrator.
Title: In the company of microbes : ten years of Small Things Considered / edited by Elio Schaechter ; artwork by Judith Schaechter.
Description: Washington, DC : ASM Press, [2016] | ?2016 | Includes bibliographical references.
Identifiers: LCCN 2016011177 | ISBN 9781555819590 (pbk.)
Subjects: LCSH: Microbiology–Blogs. | Microorganisms–Blogs.
Classification: LCC QR56 .I5 2016 | DDC 576--dc23 LC record available at http://lccn.loc.gov/2016011177

10 9 8 7 6 5 4 3 2 1

Printed in the United States of America

Address editorial correspondence to ASM Press, 1752 N St., N.W., Washington, DC 20036-2904, USA

Send orders to ASM Press, P.O. Box 605, Herndon, VA 20172, USA
Phone: 800-546-2416; 703-661-1593; Fax: 703-661-1501
E-mail: books@asmusa.org
Online: http://estore.asm.org

Cover image: Judith Schaechter
Design: Lou Moriconi

Table of Contents

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Introduction

Sometime early during 2006, ASM staff members and I began discussing ways to expand the society's communications efforts into a new area. We wanted to take better advantage of available electronic means for reaching ASM members and interested members of the public with information about microbiology. One opportunity was for ASM to launch a blog. However, blogging raised eyebrows in some circles, including the attorneys who are asked to review proposed programs of this sort. Being good lawyers, they mentioned liability issues, worrying that such an informal vehicle for communicating might prove too free-wheeling if not handled properly. Without a candidate blogger in mind, we pondered where to go next.

Meanwhile, Elio Schaechter contacted me out of the blue, saying that, in retirement, he was seeking a new project and wondered whether ASM might be interested in supporting a blog on microbiology. Instantly, our concerns over blogging liabilities vanished. Here was an eminent microbiologist and former president of ASM who was respected across the broad community of microbiologists. Don't worry, he assured us, the nooks and crannies of microbiology can provide plenty of rich material for the blog and, while it might touch on controversy, any forthcoming debates will be strictly Talmudic—(The Talmud is a combination of texts explaining the meaning of events or practices appearing in the old Testament)—not damaging to any institution or person, apart perhaps from those with especially fragile egos.

By then ASM had begun producing podcasts, and the blog that Elio conceived of doing fell under that umbrella—or, rather, onto that platform. Elio was introduced to Chris Condayan, a public communications manager at ASM, who says that Schaechter quickly proved to be a "sharp tech," meaning he soon mastered the virtual mechanics as well as the art of the blogging process. From the outset, Elio issued blog posts regularly, typically posting two items each week. He also very much molded its content, mining gems excavated from the broad expanse of the microbiological sciences.

To begin with, *Small Things Considered* was purely Elio's output, but eventually he attracted other writers and microbiologists to join him in this novel communications enterprise. The first additional steady contributor was Merry Youle, a technical writer, who approached him as an interested reader. For several years she helped to edit the postings before she began to write some of them herself. Later, several microbiologists were brought on board to broaden the scope of the blog postings but also to give Elio some hands-on help.

There was a flurry of interest after the first few postings during the second half of 2006, which subsided for a while before it gradually but steadily began building into a huge success. Over the past decade, Elio and his band

of bloggers posted more than 1,000 items on *Small Things Considered*, and those postings by now have attracted more than 2 million page views at an average of more than 600 views per day, and elicited more than 2,300 comments. Along with traditional postings, the blog now includes a Teachers Corner that caters to classroom needs. Among microbiologists, the blog is well known and much liked, but it also attracts plenty of readers outside the discipline. Further, it is so well respected that the Library of Congress has identified *Small Things Considered* as one of the first blogs in the sciences worth archiving.

The blog could only have been conceived by Elio. His store of knowledge about the science of microbiology is unequalled. He is also an unusually articulate writer and has a unique and welcoming approach to the content.

The 70 articles are divided into seven sections entitled: "The View from Here," "Accounts of the Past," "Small Wonders," "On Being a Microbiologist," "Personal Notes," "The Ways of Microbes," and "Teaching Things"

The authors, in addition to Elio, are presidents of ASM and a slew of distinguished microbiologists from all around the globe. The topics are as varied as the authors, ranging from, "Where Mathematicians and Biologists Meet" to "Bacterial Hopanoids: The Lipids That Last Forever."

This is more than just a collection of articles: it is a treasure chest of wise, amusing, and even profound statements about the ubiquity and relevance of the microbial world. As Elio notes in his introduction, "The purpose of this blog is to share my appreciation for the width and depth of the microbial activities on this planet. I will emphasize the unusual and the unexpected phenomena for which I have a special fascination."

Michael Goldberg, PhD
Executive Director Emeritus, ASM

Jeff Fox PhD
Current Topics and Feature Editor, *Microbe*

Preface

Blog Years Are Like Dog Years

How did *Small Things Considered* come about? When I retired from Tufts University some twenty years ago, I realized that for too long I had lived comfortably within the focused world of *E. coli* and its ilk. Out there, far from the lab bench, amazing and unexpected things were happening, and I was only dimly aware of some. A few of them danced in my imagination; many were just out of sight. So, I started to pay more attention to these groovy stories.

My itch of writing egged me on to look for a way to share my pleasure of exploration with others. There weren't many venues for such endeavors then, but someone whispered blog in my ear. I barely knew how to spell it, leave alone what it was, so I called Michael Goldberg, the then Executive Director of the the American Society for Microbiology (ASM), who encouraged me and put me in touch with Chris Condayan, who knew a lot about such things. Not only did Michael explain this enigmatic word to me, but he also told me that they had been talking about an ASM-sponsored blog, and, yes, if I were willing to do this, they would help me out. Chris set me up by designing the lay-out, plugging me into the proper software, and even coming up with a happy name for the blog. As an aside, when I was once interviewed on the NPR radio program *All Things Considered*, I coyly asked them if they minded our using a name derived from theirs. They said that they were actually pleased.

This blog began in 2006. Blog years are indeed like dog years, and a decade is a long time. This milestone is worth celebrating, I think. We (and I will explain the "we" right away) have been at it assiduously for all this time and, miraculously, have not missed a single one of the scheduled postings. These have been bi-weekly, Monday being devoted to longer items, Thursday to brief ones such as Talmudic Questions, Pictures Considered, or Terms of Biology. Sometime last September we reached 1000 posts, and we still doggedly continue to produce them at our habitual pace.

The "we" refers to the team that has been working with me for much of this time. Merry Youle joined me in this effort almost immediately after its inception. In the course of time, we became partners and for several years shared the responsibility for writing most of the posts, pitilessly editing each other's drafts. From this emerged a comradely friendship that continues to this day. In time, we asked others to join us, making for an interactive and productive team. The current members are Daniel Haeusser, Jamie Henzy, Gemma Reguera, and Christoph Weigel. I must mention Marvin Friedman, who would still be contributing a post a month were he still with us. Early on, I opened the pages of this blog to others, especially graduate students, who, I reckoned, could benefit from the experience. I am glad that blog-

ging by students has become a widespread activity elsewhere. Others, including notable people in the field, have presented their thoughts and opinions in STC. Nowadays most of the blog items are indeed authored by folks outside our inner group, and the choice of articles for this book reflects that.

This book was started by a prompt from Chris. For this collection I scanned our archives and focused on material that one could broadly call musings—reflections on personal and historical interactions between the writers and microbes. A few of the pieces included fall outside this scope and are mostly about unusual discoveries. Why did I not opt for more science-oriented stuff? Two reasons: one is that their appeal would be narrower; the other is that such material becomes rapidly dated. And besides, wouldn't you want to hear what questions and puzzles still animate microbiologists, what they think about both the past and the future of the field?

Our 1000 posts have garnered some two million views. I guess that's something to brag about, but more to the point is the enjoyment that this effort has brought me. I have always had something of a naturalistic bone in my body. Being obliged to work at the bench, pleasurable though it has been, kept me from relishing the small wonders that are "out there," where there is a never-ending pageant of astounding variations on the theme of microbial life. In old age, such hankerings are to be indulged and such wanderings to be treasured. They help provide answers to some of the eternal questions that I (and you too, dear reader) have been asking intermittently since adolescence. So, my deepest thanks to all who have given me this jewel of an opportunity but most of all, to the small things that are waiting to be considered.

Elio Schaechter
October 2015
San Diego, California, USA

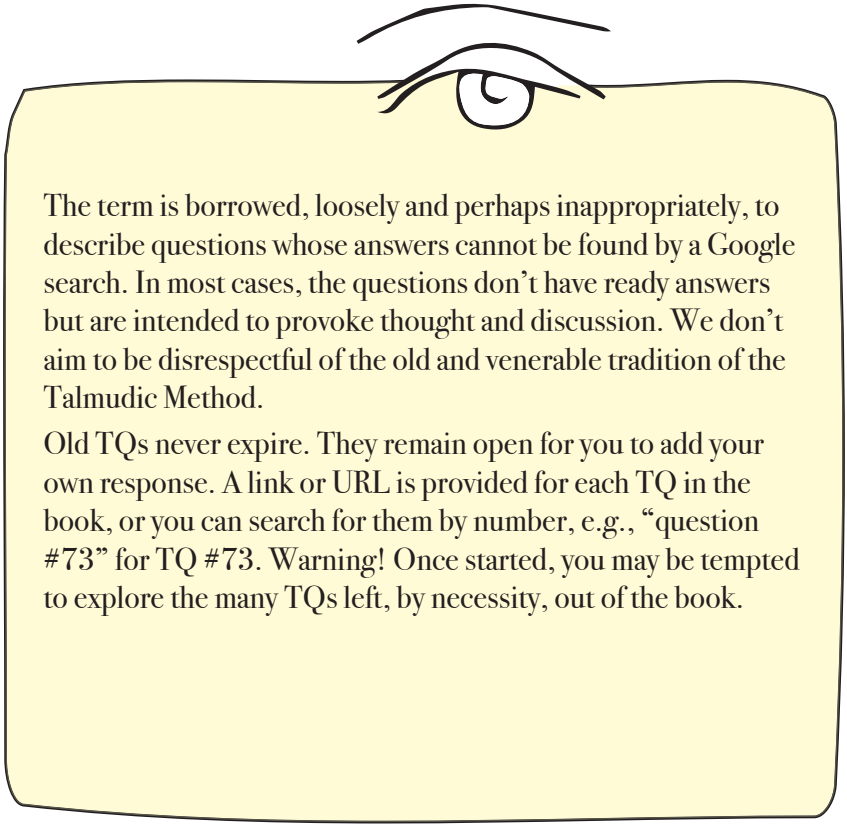
Acknowledgments

My thanks go to all who have contributed to the blog over the years and have helped make exciting stories accessible to a wide public. I single out Merry Youle, who was my partner for several years and a friend. She helped me in every way imaginable, from the choice of topics, to doing the wisest of editing, to providing me with a moral compass, to holding my hand (at a distance, as she lives in Hawaii, I in California). I thank my other collaborators on this endeavor: Gemma Reguera, Daniel Haussler, Jamie Henzy, and, early on, Mark Martin and Welkin Johnson. Christoph Weigel needs to be acknowledged in a special way for his extraordinary contributions to both the blog's content and format. Also, I thank the late Marvin Friedman who, for many years, was another faithful contributor. All these persons did more than supply material: they participated in thinking about ways this blog could better fulfill its purpose. They have all done it with verve, passion, and great insights. I have been very lucky indeed.

I thank the American Society for Microbiology (ASM) for sponsoring the blog, especially the Communications staff directed by Erika Shugart. Chris Condayan generously and imaginatively supported this effort from the very beginning and has been a source of help and encouragement ever since. Andréa Gwartney did a superb job dealing with the layout and organization of the material. Ray Ortega later took charge of producing each issue of the blog, using a keen eye and warm heart in order to achieve this blog's intended purposes. All of these persons have treated their work as a labor of love.

I thank my wife, Edith, for her support. She is not a scientist but has played a huge role in everything else it takes to carry out such an activity. I also thank my daughter Judith for allowing me to use her drawings. She is a renowned stained glass artist whose doodles are often of imaginary protists and diatoms. I never expected to see both our names on the cover of the same book.

What do we mean by a Talmudic Question?



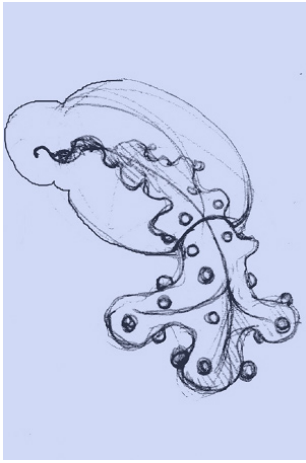
The term is borrowed, loosely and perhaps inappropriately, to describe questions whose answers cannot be found by a Google search. In most cases, the questions don't have ready answers but are intended to provoke thought and discussion. We don't aim to be disrespectful of the old and venerable tradition of the Talmudic Method.

Old TQs never expire. They remain open for you to add your own response. A link or URL is provided for each TQ in the book, or you can search for them by number, e.g., "question #73" for TQ #73. Warning! Once started, you may be tempted to explore the many TQs left, by necessity, out of the book.

PART 1

The View from Here

I invited experienced microbiologists to share some of their musings, and I added a few of my own.



1

Of Ancient Curses, Microbes, and the ASM

by Bonnie L. Bassler

On July 1, 2010, when I started my term as ASM president, I was reminded of three ominous curses of dubious ancient origin:

1. May you live in interesting times.
2. May you come to the attention of those in authority.
3. May you find what you are seeking.

May you live in interesting times: Clearly, these times qualify. Microbes will be at the heart of solutions to our most pressing problems: the environment, food, energy, and health. The BP oil spill began on day –79 of my term. Microbes are coming to the rescue, and ASM expertise is on the scene Let us hope that lessons have been learned. In his inauguration address, President Obama promised to "*restore science to its rightful place*." It may be happening. The National Academy of Science's Board on Life Sciences recently released its report: *A New Biology for the Twenty-First Century*. The US Cabinet Secretaries of Energy and Agriculture requested a series of workshops to discuss how to implement the new biology. A first workshop, focused on food and fuel, was held in DC last month, and I was invited to participate (day –27 of my term). Workshop members were asked to develop scientific challenges for the decade to be proposed to Congress for funding. Together with several other ASM members in attendance, I strongly advocated the understanding and appropriate use of microbes to synthesize new fuels, clean up the

environment, optimize crop production, etc. Our rallying sound bite: microbes, the world's only unlimited renewable resource!

May you come to the attention of those in authority: On May 20, with quite some fanfare, *Science* published a manuscript: *Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome*. On that same day (day –42 of my term) the ASM Public and Scientific Advisory Board (PSAB) released a position statement offering a balanced perspective on the manuscript, the status of the field of synthetic biology, and its regulation. A number of ASM members, including myself, gave expert opinions in newspapers, on the radio, and on TV. President Obama requested his Presidential Commission for the Study of Bioethical Issues to undertake a study of the implications of this scientific research and other advances that may lie ahead in this field. I will testify at the first Commission hearing on July 8 (day +8 of my term—at last we're into positive numbers!). I feel well equipped to represent us. Last year I was the organizer and chair of the National Academies of Sciences Keck Futures Conference on Synthetic Biology. I continue to learn about new developments in the field, and I am expertly advised by our PSAB staff, our new PSAB Chair Roberto Kolter, and other knowledgeable ASM members. My specific role is to compare and contrast the engineering perspective with that of the biological and genetic sciences, and to explain how approaches represented by synthetic biology differ from other approaches to biological manipulation. I will also address what has been accomplished and what is likely to be accomplished in this field and what I think are important obstacles to the advancement of synthetic biology.

May you find what you are seeking: Over this past year (day –365 to day 0) as president-elect, I got to know the Society inside and out. I learned what remarkable accomplishments 40,000 volunteers can achieve. I saw our members donate huge blocks of time for the good of our discipline and the health of our planet. I became fully convinced that collectively we have the potential and the expertise to make the world healthier, to enable a sustainable relationship with our environment, and to ensure the promise and prominence of science and technology in our culture. It has been a magical and eye-opening year. I am beginning to understand the vast breadth and depth of this organization and the position of its members in leading the nation and the world in all in matters touched by microbes.

There's nothing like a few ominous curses to get the blood flowing. I am eagerly looking forward to this coming year with the hope that I can make significant contributions to the ASM and to our community at large. I will do my best to further enhance our reputation in public policy, education, outreach, and scientific advancement. Now at day +1 and counting, I look forward to meeting you!

We have a tradition of hosting a few reflections from the incoming president of the ASM.

Bonnie Bassler is the Squibb Professor of Molecular Biology at Princeton University and a Howard Hughes Medical Institute Investigator. She is a fellow of the American Academy of Microbiology and a member of both the National Academy of Sciences and the American Academy of Arts and Sciences.

July 1, 2010

bit.ly/1LAnyRd

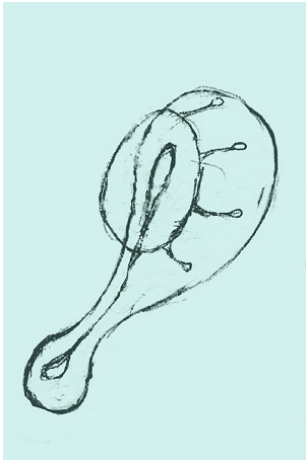
#86

by Elio

Given that so many kinds of bacteria are intimately associated with animals and plants, why are so relatively few pathogenic?

April 12, 2012

bit.ly/1NRFuN5



2

The View from Here: The Evolution of the Genetic Code

by Charles Yanofsky

Although the genetic code is well established, a very exciting unsolved problem is discovering how codons were related to amino acids in the evolution of protein synthesis. How did a tRNA and a tRNA synthetase first evolve, and what was their ancestral source? How were the genes for the first tRNA and tRNA synthetase duplicated, and how was their specificity varied? Can we offer any explanation for why there are two classes of tRNA synthetases? Can one predict which tRNAs evolved from one another? Similarly, can we predict which tRNA synthetases evolved from an existing tRNA synthetase?

A related series of exciting experiments would be to attempt to reproduce some evolutionary events and determine how many mutational changes it would take—and where—to evolve a tRNA synthetase with new specificity from an existing synthetase. Suppression studies many years ago showed that tRNAs may acquire new decoding specificity following single mutational changes, but synthetase suppressors were not recovered, as I recall. Also, we now know that synthetases recognize both the anticodon and acceptor end sequence of each tRNA. Is this consistent with what is known about suppressing tRNAs?

Reference

Carter CW Jr. 2008. Whence the genetic code? Thawing the 'Frozen Accident'. *Heredity* **100**:339–340.

Charles Yanofsky is Professor Emeritus of Biological Sciences at Stanford University and a 2003 recipient of the National Medal of Science.

May 8, 2008

bit.ly/1Gfy8R5

#19

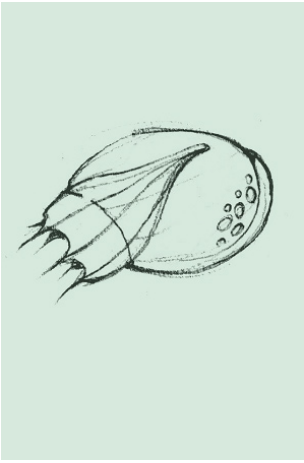
by Elio

You are stranded on a desert island. During a walk on the beach, you stub your toe against a bottle, which rolls against a rock and breaks. A genie is liberated, eager to grant you one wish. You ask for a microbiological laboratory fully equipped to your specifications. The genie grants you that but with the condition that you can study only one sample. What sample would you collect for study, what would you do with it, and why?

July 8, 2007

bit.ly/1LHnXVC

3



Microbes Touch Everything

By Tim Donohue

As I wheeled my bag away from the Convention Center in New Orleans after the 115th General Meeting, I noticed its ASM luggage tag, which states "*Microbes Touch Everything.*" This simple line is a perfect summary of the importance of the microbial sciences and the core mission of ASM to promote and advance this field. In history there are many examples of times when the right confluence of people and technology has led to events that rapidly push back frontiers. Two examples, one old, one of our time—Leeuwenhoek seeing animalcules through his lens and the elucidation of the structure of DNA and the genetic code—both transformed science and opened new fields of exploration. The microbial sciences are now poised to enter a renaissance that is based on interdisciplinary approaches and new technologies.

In order to take advantage of this scientific moment, we must reach out to our colleagues in other fields. At the General Meeting I heard many talks that highlighted the importance of bringing new scientific disciplines into the microbial sciences. Du-ring his opening lecture, Pieter Dorrestein shared his exciting work to understand the activities of microbial communities using mass spectrometry. He began and ended his talk by noting that he is a chemist, but that his work is in the microbial sciences. Minyoung Chun of the Kavli Foundation reflected on the foundation's interest in microbiology during the president's lecture. She noted that Kavli has historically funded researchers focused on astronomy, nanoscience, and neuroscience. In the past year they have held a series of symposia focused on

the microbiome because they repeatedly heard from their physical scientists that microbiology is one of the most exciting new frontiers and thus is worth exploring. From looking for alien life to connecting the brain to the gut microbiome, microbiologists are now involved in a huge number of other fields. Clearly, our attention to interdisciplinary science must continue to grow.

Parallel to the expansion into the microbial sciences of traditionally separate fields is the boom of new technologies that are making it easier to see the unseen and contribute to understanding the world around us. For decades microbiologists were limited to studying the small fraction of the organisms that were culturable. The development of extraordinary sequencing techniques has enabled us to begin to study the other 99 percent, the microbial "dark matter" that is all around us. This technology holds great promise for the discovery of new drugs and such needed products as biofuels. Think of CRISPR-Cas as another discovery whose applications hold great promise. The ability to readily move genes into new positions is proving to be a boon to what was called the biotech industry when I was a student.

One of the most obvious areas of study that creates interdisciplinary research and new technology is that of the microbiome. Microbiologists are joining with computer scientists, ecologists, engineers, imaging experts, plus others to understand the complex ecosystems of the microbes that touch us or impact our environment in yet unknown ways. These efforts have attracted the attention of the White House, which recently sent out a request for an account of the federally-funded work in this area. Microbiome discoveries garner significant attention from the news media and the public as well.

We can work as a community to make a microbial sciences renaissance occur, or we can let the opportunity pass us by, slowing down the progress that has been made. If we become too insular, overhype our findings, and allow overly restrictive regulations to impede progress, then we have mainly ourselves to blame. As microbial sciences research becomes more complex and interdisciplinary, we must learn the best practices of team science in order to make collaborations work successfully.

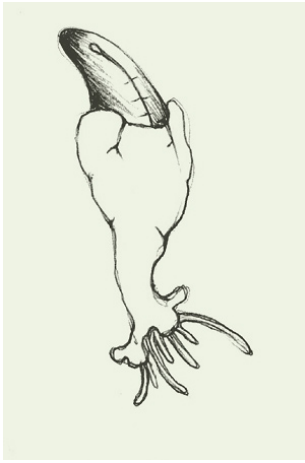
The need to articulate the risk, benefits, and need for basic science was made clear by AAAS president and ex-Congressman Rush Holt in his president's forum speech on Monday. There have been calls not only from policy makers, but from microbiologists as well to look into the impact, ethics, and regulation of the use of microbes. While we may not always agree on the details, we must each participate in the ongoing dialogue about the progress that can be made in the responsible conduct of science. I call upon you to look outward to your colleagues, your community, and the ASM to explore the possibilities that the microbial sciences hold and to help push our field forward. Success in this endeavor is needed for us to truly understand how and why "*Microbes Touch Everything*."

We continue our tradition of hosting a few reflections from presidents of the ASM.

Tim Donohue is a professor at The University of Wisconsin at Madison and a past president of the American Society for Microbiology.

July 30, 2015

bit.ly/1LleAJS



4

Getting a Handle on Cell Organization

by Franklin M. Harold

Structural organization is one of the most conspicuous features of cells, and possibly the most elusive. No one really doubts that cell functions commonly require that the right molecules be in the right place at the right time, or that spatial organization is what distinguishes a living cell from a soup of its molecular constituents. But the tradition that has dominated biological research for the past century mandates a focus on the molecules, and so our first step is commonly to grind the exquisite architecture of the living cell into a pulp. Few molecular scientists have asked whether anything irretrievable is lost by this brutal routine. Such questions as how molecules find their proper place in a framework of orders of greater magnitude, or how spatial order is transmitted from one generation to the next, have been largely neglected until recently.

Two current and quite excellent short reviews afford an entry into the wilderness. Eric Karsenti takes an historical approach to the role of self-organization in creating order on the cellular scale. The physical principles are arcane, but some aspects are actually quite familiar. We have known for half a century that supra-molecular complexes often arise by self-assembly, without any input of either information or energy; examples include lipid bilayer membranes, ribosomes, microtubules, S-layers, and virus particles. But the scope of self-organization has been greatly enlarged in recent years by the discovery that an array of dynamic structures can be generated in the presence of an energy source, usually ATP or GTP. The mitotic

spindle of eukaryotes has been identified as a self-organizing machine; the endomembrane system may be another. Like self-assembly, self-construction (my term) requires no external source of information, but it does entail continual energy consumption. In a complementary article, Allen Liu and Daniel Fletcher survey a selection of efforts to reconstitute cellular functions in simplified systems, starting with cell-free extracts or purified proteins. Ingenious experimenters have managed to reconstitute the essentials of actin-based motility, membrane protrusion, the oscillatory system that localizes the midpoint of bacterial cells, and now also the contraction of the Z-ring. Though much remains to be learned, it is safe to conclude that the lower levels of cellular order, at least, are products of pure chemistry: they arise by interactions among the molecular constituents in ways that require the cell as a whole to supply energy and a permissive environment, but no spatial instructions.

This is excellent science, which takes us some way towards bridging the gulf between nanometer-sized molecules and cells in the range from micrometers to millimeters. It also extends the genome's reach deep into cellular structure. In a self-organizing system, the "instructions" must be wholly inherent in the molecular parts, and ultimately derive from the corresponding genes. It is the genome that specifies the architecture of the mitotic spindle, not explicitly but indirectly: the form and even functions of the spindle are implied in the structure of the spindle proteins, and in their interactions. And if the spindle can be envisaged as a creature of self-organization, why not the entire cell? Yes, indeed—but as we ascend the hierarchy of biological organization, the meaning assigned to self-organization and its underlying mechanisms undergo significant changes. Cells do not construct themselves from pre-fabricated standard parts; instead, they grow. And that mode of self-organization is not purely chemical, for it must produce parts that have biological functions, performed in the service of a larger entity that can compete and thrive in the wide world.

We are quite well informed about just how cells grow, and it is clear now that they do so by modeling themselves upon the existing structural framework, which is thereby transmitted to the next generation. To be sure, all the macromolecules involved in this sort of self-organization are gene-specified, but spatial order is not. There appear to be very few individual genes that prescribe dimensions,

position, or orientation on the cellular scale. Instead, thanks to the ways in which cells grow, spatial cues are sometimes inherited in a manner quite independent of genes, (a well-established phenomenon known as "structural inheritance." The form and organization of cells thus stem from two distinct informational roots: the genomic instructions that specify the parts, and the continuity of cellular architecture that guides their placement. Specified proteins and cellular guidelines operate synergistically, reinforcing each other to generate form and organization. As Rudolf Virchow might have said, it takes a cell to make a cell.

Evidence to support such a holistic view of what happens during growth is scattered, but continues to accumulate. Let's glance at some examples. First, while many sub-cellular structures can be envisaged as products of self-construction from preformed parts, others cannot. A familiar instance is the peptidoglycan wall of bacteria, which consists of a network as large as the cell, made up of covalently-linked subunits. Enlargement during growth calls for extensive cutting, splicing, and cross-linking, even while keeping the wall physically continuous from one generation to the next. Second, even self-organizing structures must do so in a manner that ensures their correct placement in cellular space. A particularly neat example comes from recent work on the role of microtubules in cell morphogenesis of the fission yeast, *Schizosaccharomyces pombe* (reviewed by Martin). Microtubules define the poles of elongating cells by depositing there various members of the Tea complex, which in turn recruit additional factors. Cells of a certain mutant, orb6, grow as spheres even though they possess all this machinery. When, however, the mutant cells are grown in microfluidic channels that force them back into the cylindrical shape, the normal longitudinal orientation of the microtubules recovers, and so does deposition of polarity factors at the poles (Terenna et al.). Clearly, the microtubule system and cell form collaborate to organize the cell. Just how this comes about is uncertain, but we can borrow a clue from another admirable study, this one in *Bacillus subtilis*. Ramamurthi et al. found that the peripheral membrane protein SpoVM localizes to a particular patch of membrane during sporulation by recognizing its curvature; perhaps microtubule ends do likewise.

All this makes good sense, at least to me, but it reopens the question how, and indeed whether, the genome specifies cell morphology and organization. The classical conception, which has been articulated by such luminaries as August Weismann, François Jacob,