Using Technology to Study Cellular and Molecular Biology

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National Center for Research Resources

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Foreword

This curriculum supplement, from *The NIH Curriculum Supplement Series*, brings cutting-edge medical science and basic research discoveries from the laboratories of the National Institutes of Health (NIH) into classrooms. As the largest medical research institution in the United States, NIH plays a vital role in the health of all Americans and seeks to foster interest in research, science, and medicine-related careers for future generations. NIH's Office of Science Education (OSE) is dedicated to promoting science education and scientific literacy.

We designed this curriculum supplement to complement existing life science curricula at both the state and local levels and to be consistent with *National Science Education Standards*.[1] It was developed and tested by a team composed of teachers, scientists, medical experts, and other professionals with relevant subject-area expertise from schools and institutes from across the country; and by NIH scientists and curriculum-design experts from Biological Sciences Curriculum Study (BSCS), Edge Interactive, and SAIC. The authors incorporated real scientific data and actual case studies into classroom activities. A three-year development process included geographically dispersed field tests by teachers and students.

The structure of this module enables teachers to effectively facilitate learning and stimulate student interest by applying scientific concepts to real-life scenarios. Design elements include a conceptual flow of lessons based on BSCS's 5E Instructional Model of Learning, multisubject integration emphasizing cutting-edge science content, and built-in assessment tools. Activities promote active and collaborative learning and are inquiry-based to help students develop problem-solving strategies and critical thinking.

Each curriculum supplement comes with a complete set of materials for both teachers and students, including printed materials, extensive background and resource information, and a Web site with interactive activities. The supplements are distributed at no cost to teachers across the United States. All materials may be copied for classroom use but may not be sold. We welcome feedback from our users. For a complete list of curriculum supplements, updates, availability and ordering information, or to submit feedback, please visit our Web site at *http://science.education.nih.gov* or write to

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We appreciate the valuable contributions of the talented staff at BSCS, Edge Interactive, and SAIC. We are also grateful to the NIH scientists, advisors, and all other participating professionals for their work and dedication. Finally, we thank the teachers and students who participated in focus groups and field tests to ensure that these supplements are both engaging and effective. I hope you find our series a valuable addition to your classroom and wish you a productive school year.

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1 In 1996, the National Academy of Sciences released the *National Science Education Standards*, which outlines what all citizens should understand about science by the time they graduate from high school. The *Standards* encourages teachers to select major science concepts that empower students to use information to solve problems rather than stressing memorization of unrelated information.

About the National Institutes of Health

Begun as the one-room Laboratory of Hygiene in 1887, the National Institutes of Health (NIH) today is one of the world's foremost medical research centers and the federal focal point for health research in the United States.

Mission and Goals

The NIH mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. The goals of the agency are to

- foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for advancing significantly the nation's capacity to protect and improve health;
- develop, maintain, and renew scientific resources—both human and physical—that will ensure the nation's ability to prevent disease;
- expand the knowledge base in medical and associated sciences in order to enhance the nation's economic well-being and ensure a continued high return on the public investment in research; and
- exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

NIH works toward meeting those goals by providing leadership, direction, and grant support to programs designed to improve the health of the nation through research in the

- causes, diagnosis, prevention, and cure of human diseases;
- processes of human growth and development;
- biological effects of environmental contaminants;
- understanding of mental, addictive, and physical disorders; and
- collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists.

Organization

Composed of 27 separate institutes and centers, NIH is one of eight health agencies of the Public Health Service within the U.S. Department of Health and Human Services. NIH encompasses 75 buildings on more than 300 acres in Bethesda, Md., as well as facilities at several other sites in the United States. The NIH budget has grown from about $300 in 1887 to more than $27.8 billion in 2004.

Research Programs

One of NIH's principal concerns is to invest wisely the tax dollars entrusted to it for the support and conduct of this research. Approximately 82 percent of the investment is made through grants and contracts supporting research and training in more than 2,000 research institutions throughout the United States and abroad. In fact, NIH grantees are located in every state in the country. These grants and contracts make up the NIH Extramural Research Program.

Approximately 10 percent of the budget goes to NIH's Intramural Research Programs, the more than 2,000 projects conducted mainly in its own laboratories. These projects are central to the NIH scientific effort. First-rate intramural

scientists collaborate with one another regardless of institute affiliation or scientific discipline and have the intellectual freedom to pursue their research leads in NIH's own laboratories. These explorations range from basic biology to behavioral research, to studies on treatment of major diseases.

Grant-Making Process

The grant-making process begins with an idea that an individual scientist describes in a written application for a research grant. The project might be small, or it might involve millions of dollars. The project might become useful immediately as a diagnostic test or new treatment, or it might involve studies of basic biological processes whose clinical value may not be apparent for many years.

Each research grant application undergoes peer review. A panel of scientific experts, primarily from outside the government, who are active and productive researchers in the biomedical sciences, first evaluates the scientific merit of the application. Then, a national advisory council or board, composed of eminent scientists as well as members of the public who are interested in health issues or the biomedical sciences, determines the project's overall merit and priority in advancing the research agenda of the particular NIH funding institutes.

About 38,500 research and training applications are reviewed annually through the NIH peer-review system. At any given time, NIH supports 35,000 grants in universities, medical schools, and other research and research training institutions, both nationally and internationally.

NIH Nobelists

The roster of people who have conducted NIH research or who have received NIH support over the years includes some of the world's most illustrious scientists and physicians. Among them are 115 winners of Nobel Prizes for achievements as diverse as deciphering the genetic code and identifying the causes of hepatitis.

Five Nobelists made their prize-winning discoveries in NIH laboratories. You can learn more about Nobelists who have received NIH support at *http://www.nih.gov/about/almanac/nobel/index.htm*.

Impact on the Nation's Health

Through its research, NIH has played a major role in making possible many achievements over the past few decades, including

- Mortality from heart disease, the number one killer in the United States, dropped by 36 percent between 1977 and 1999.
- Improved treatments and detection methods increased the relative five-year survival rate for people with cancer to 60 percent.
- With effective medications and psychotherapy, the 19 million Americans who suffer from depression can now look forward to a better, more productive future.
- Vaccines are now available that protect against infectious diseases that once killed and disabled millions of children and adults.
- In 1990, NIH researchers performed the first trial of gene therapy in humans. Scientists are increasingly able to locate, identify, and describe the functions of many of the genes in the human genome. The ultimate goal is to develop screening tools and gene therapies for the general population for cancer and many other diseases.

For more information about NIH, visit http://www.nih.gov.

About the National Center for Research Resources

The National Center for Research Resources (NCRR) is a component of the National Institutes of Health (NIH), one of the world's foremost biomedical research organizations. The institutes and centers that compose NIH fund biomedical research to uncover new knowledge that will lead to better health for everyone in the nation. Among the NIH institutes and centers, NCRR has a unique role. Rather than supporting studies of specific diseases or disorders, NCRR supports programs that ensure that essential tools, materials, specialized facilities, and resources for infrastructure and manpower development are accessible to biomedical researchers throughout the nation. In this way, NCRR enables research in many areas of health and complements the missions of the NIH categorical institutes. NCRR's diverse array of resources is concentrated in four divisions:

Biomedical Technology Research and Research Resources: A large network of Biomedical Technology Resource Centers provides the research community nationwide with the newest and most advanced technologies and techniques. Core scientists at these centers collaborate in multidisciplinary investigations and train visiting researchers to apply these technologies and techniques to basic and clinical studies. In addition, NCRR provides institutional grants to purchase expensive state-of-the-art and high-end instrumentation to be used by a number of investigators on a shared basis.

Clinical Research Resources: A national network of General Clinical Research Centers offers NIH-supported investigators and others specialized research environments that are professionally staffed, have state-of-the-art technologies and Web-based networks, and provide collaborative research opportunities. NCRR also supports networks of National Gene Vector Laboratories and Human Islet Cell Resource Centers, a resource for normal and diseased human tissue for research, and science education for K–12 students and the public.

Comparative Medicine: Animal models and colonies (mammalian and nonmammalian), genetic stocks, and biological materials—such as cell lines, tissues, and organs—help meet NIH-supported investigators' resource needs. In particular, the NCRR network of eight National Primate Research Centers is a valuable resource for investigations of human health and disease.

Research Infrastructure: Diverse grant programs help build, expand, and strengthen the nation's biomedical research environment by developing research infrastructure and faculty capacity at minority institutions that award doctorates in the health or health-related sciences; improving biomedical and behavioral research through an NIH-wide program of matching grants for construction and renovation of research facilities; and increasing competitiveness of institutions from states with limited NIH support.

For more information about research resources and resource-related funding opportunities, visit the National Center for Research Resources Web site at *http://www.ncrr.nih.gov.*

Introduction to *Using Technology to Study Cellular and Molecular Biology*

The abilities to develop and use technology are inherent human characteristics. We recognize problems and look for solutions. Technology makes our lives easier and more comfortable. At the same time, critical research technologies have advanced scientific discovery. Where scientists once gazed in awe at individual cells and microorganisms, we now can view the electron clouds of individual atoms and reconstruct detailed three-dimensional structures of biological molecules, such as proteins, and biological structures, such as ribosomes. As the depth and breadth of scientific knowledge have increased, human health and our quality of life have improved.

What Are the Objectives of the Module?

Using Technology to Study Cellular and Molecular Biology has several objectives. The first is to help students understand that technology is a means of solving a problem. As a consequence, students realize that technologies affect all facets of our lives and that technology relates to more than computers.

The second objective is to allow students to investigate how technology is used to deepen and broaden our knowledge of cellular and molecular biology. Lessons in this module help students sharpen their skills in observation, critical thinking, experimental design, and data analysis. They also make connections to other disciplines such as English, history, mathematics, and social science.

The third objective is to convey to students the purpose of scientific research. Ongoing research affects how we understand the world around us and provides the foundation for improving our choices about our personal health and the health of our community. With this module, students experience how science provides evidence that can be used to understand and treat human disease. The National Center for Research Resources believes that education is an important way to accomplish its mission, which includes helping the public understand the importance of technology use and development to health.

The lessons in this module encourage students to think about the relationships among knowledge, choice, behavior, and human health in this way:

Knowledge (what is known and not known) + Choice = Power

Power + Behavior = Enhanced Human Health

The final objective of this module is to encourage students to think in terms of these relationships now and as they grow older.

Why Teach the Module?

High school biology classes offer an ideal setting for integrating many areas of student interest. In this module, students participate in activities that integrate inquiry science, human health, mathematics, and the interweaving of science, technology, and society. The real-life context of the module's classroom lessons is engaging for students, and the knowledge gained can be applied immediately to students' lives.

"Lesson 3 was a great inquiry experience. Students

enjoyed the activity and at the same time, learned how to apply what they know about technology. The scale activity really got students thinking about the size of the cell and what is in the cell. This was a wow activity."—Field-Test Teacher

"The activities made us think. We figured out things ourselves, and we actually did stuff instead of just reading."—Field-Test Student

What's in It for the Teacher?

Using Technology to Study Cellular and Molecular Biology meets many of the criteria by which teachers and their programs are assessed.

- The module is **standards based** and meets science content, teaching, and assessment standards as expressed in the *National Science Education Standards*. It pays particular attention to the standards that describe what students should know and be able to do with respect to **scientific inquiry**.
- It is an **integrated** module, drawing most heavily from the subjects of science, social science, mathematics, and health.
- The module has a Web-based **technology component** on which there is an interactive database and simulations.
- The module includes built-in **assessment tools**, which are noted in each of the lessons with an assessment icon.

In addition, the module provides a means for **professional development**. Teachers can engage in new and different teaching practices like those described in this module without completely overhauling their entire program. In *Designing Professional Development for Teachers of Science and Mathematics*, the authors write that replacement modules such as this one "offer a window through which teachers get a glimpse of what new teaching strategies look like in action."[16] By experiencing a short-term unit, teachers can "change how they think about teaching and embrace new approaches that stimulate students to problem solve, reason, investigate, and construct their own meaning for the content." The use of a supplemental unit such as this module can encourage reflection and discussion and stimulate teachers to improve their practices by focusing on student learning through inquiry.

The following table correlates topics often included in the high school biology curriculum with the major concepts presented in this module. This information is presented to help teachers make decisions about incorporating this material into the curriculum.

If you have any questions about the supplement, please contact the NIH Office of Science Education at *supplements@science.education.nih.gov.*

Correlation of *Using Technology to Study Cellular and Molecular Biology* to High School Biology Topics

Topics	Lesson 1	Lesson 2	Lesson 3	Lesson 4
The development of new technologies is continuous, and the ability to develop new technologies is characteristic of humans.	✔			✔
Technology provides a means of solving a problem.	✔	✔	✔	✔
Biological structures differ in size.	✔			
Different technologies are used to study biological structures of different sizes.		✔	✔	
Biologists use microscopes to study cells.			✔	✔
Proteins are important biological molecules. Their structure is related to their function.			✔	✔
Science and technology influence, and are influenced by, society.	✔			✔

Implementing the Module

The four lessons in this module are designed to be taught in sequence for approximately one week as a replacement for a part of the standard curriculum in high school biology. The following pages offer general suggestions about using these materials in the classroom; you will find specific suggestions in the procedures provided for each lesson.

What Are the Goals of the Module?

Using Technology to Study Cellular and Molecular Biology is designed to help students reach these major goals associated with scientific literacy:

- to understand a set of basic scientific principles related to the nature and role of technology in biological science and to the effects of technology on human health;
- to experience the process of scientific inquiry and develop an enhanced understanding of the nature and methods of science;
- to recognize the role of science in society and the relationship between basic science and human health; and
- to help prepare high school biology students for the technological world they will inherit.

What Are the Science Concepts and How Are They Connected?

The lessons are organized into a conceptual framework that allows students to move from what they already know about technology, some of which may be incorrect, to gaining a scientific perspective on the nature of technology and its importance to science and to their lives. Students begin learning about technology by developing their own definition of it and learning about scale (*What Is Technology?*). Students continue to explore the concept of scale and investigate resolution (*Resolving Issues*). An investigation of how technologies can be used to solve scientific problems related to human health (*Putting Technology to Work*) allows students to gain a deeper understanding of technology's importance to our lives. The final lesson, *Technology: How Much Is Enough?*, allows students to consider the current state of technology and design new technologies to answer questions of relevance to cellular and molecular biology. The following two tables illustrate the science content and conceptual flow of the classroom lessons.

Science Content of the Lessons

Lesson	Science Content
Lesson 1	Technology; scale
Lesson 2	Resolution
Lesson 3	Microscopy; X-ray crystallography; using technology to understand and solve health-related problems
Lesson 4	History of technology development; development of new technologies

Conceptual Flow of the Lessons

Lesson	Learning Focus*	Major Concept
Lesson 1 *What Is Technology?*	Engage Explore Explain	Technology is a body of knowledge used to create tools, develop skills, and extract or collect materials. It is also the application of science (the combination of the scientific method and material) to meet an objective or solve a problem. Scale is a way to represent the relationship between the actual size of an object and how that size is characterized, either numerically or visually.
Lesson 2 *Resolving Issues*	Explore Explain	It is important to identify the right tool (technology) for the job. An important consideration is technology's ability to resolve structural details of biological objects. Two objects can be resolved if they are illuminated with radiation (that is, a probe) of wavelength (that is, size) that is not larger than the distance separating the objects. Generally, the smaller the probe used, the greater the structural detail, or resolution, that results. Detailed structural knowledge about biological objects requires information obtained in three dimensions, not just two.
Lesson 3 *Putting Technology to Work*	Explore Explain Elaborate	Technologies differ in their resolving capabilities, thus providing different information about an object. Solving a problem requires an appropriate technology or series of technologies. Technology provides valuable tools for solving scientific problems of relevance to human health.
Lesson 4 *Technology: How Much Is Enough?*	Evaluate	New technologies are developed, and old technologies are improved and refined, continuously. This must be done to meet the demands created by new and existing problems.

*See *How Does the 5E Instructional Model Promote Active, Collaborative, Inquiry-Based Learning?* on page 9.

How Does the Module Correlate to the *National Science Education Standards*?

Using Technology to Study Cellular and Molecular Biology supports you in your efforts to reform science education in the spirit of the National Research Council's 1996 *National Science Education Standards* (*NSES*). The content of the module is explicitly standards based. Each time a standard is addressed in a lesson, an icon appears in the margin along with the applicable standard. The following chart lists the specific content standards that this module addresses.

Content Standards: High School

Standard A: **As a result of activities in grades 9–12, all students should develop**	**Correlation to** ***Using Technology to Study Cellular and Molecular Biology***
Abilities necessary to do scientific inquiry	
• Identify questions and concepts that guide scientific investigations.	Lessons 1, 2, 3, 4
• Design and conduct a scientific investigation.	Lesson 3
• Use technology and mathematics to improve investigations and communications.	Lessons 2, 3, 4
• Formulate and revise scientific explanations and models using logic and evidence.	Lesson 3
• Recognize and analyze alternative explanations and models.	Lessons 1, 3
• Communicate and defend a scientific argument.	Lessons 3, 4
Understandings about scientific inquiry	
• Scientists usually inquire about how physical, living, or designed systems function.	Lessons 3, 4
• Scientists conduct investigations for a wide variety of reasons, such as to discover new aspects of the natural world, to explain observed phenomenon, or to test conclusions of prior investigations or predictions of current theories.	Lesson 3
• Scientists rely on technology to enhance gathering and manipulating data.	Lessons 2, 3, 4
• Mathematics is essential in all aspects of scientific inquiry.	Lessons 1, 4
• Scientific explanations must adhere to criteria.	Lesson 3
• New knowledge and methods emerge from different types of investigations and public communication among scientists.	Lessons 3, 4
Standard B: **As a result of their activities in grades 9–12, all students should develop understanding of**	
Structure and properties of matter	
• The physical properties of molecules are determined by the structure of the molecule.	Lesson 3
Standard C: **As a result of their activities in grades 9–12, all students should develop understanding of**	
The cell	
• Cells have particular structures that underlie their functions.	Lesson 3

Standard E: **As a result of their activities in grades 9–12, all students should develop understanding of**	
Abilities of technological design	
• Identify a problem or design an opportunity.	Lessons 1, 2, 3, 4
• Implement a proposed solution.	Lessons 2, 3
• Evaluate the solution and its consequences.	Lessons 2, 3, 4
• Communicate the problem, process, and solution.	Lessons 1, 2, 3, 4
Understandings about science and technology	
• Many scientific investigations require contributions from different disciplines, including engineering.	Lessons 1, 2, 3, 4
• Science often advances with new technologies.	Lessons 1, 4
• Creativity, imagination, and a good knowledge base are all required in the work of science and engineering.	Lessons 1, 4
• Scientific inquiry is driven by the desire to understand the natural world, and technological design is driven by the need to meet human needs and solve human problems.	Lessons 1, 4
Standard F: **As a result of their activities in grades 9–12, all students should develop understanding of**	
Science and technology in local, national, and global challenges	
• Science and technology are essential social enterprises.	Lessons 1, 4
• Progress in science and technology can be affected by social issues and challenges.	
Standard G: **As a result of their activities in grades 9–12, all students should develop understanding of**	
Science as a human endeavor	
• Individuals and teams have contributed and will continue to contribute to the scientific enterprise.	Lessons 1, 2, 3, 4
• Scientists have ethical traditions that value peer review, truthful reporting about methods and investigations, and making public the results of work.	Lesson 3
• Scientists are influenced by societal, cultural, and personal beliefs. Science is a part of society.	Lessons 1, 4
Nature of scientific knowledge	
• Science distinguishes itself form other ways of knowing and from other bodies of knowledge through the use of empirical standards, logical arguments, and skepticism.	Lesson 3

• Scientific explanations must meet certain criteria such as consistency and accuracy.	Lesson 3
• All scientific knowledge is subject to change as new evidence becomes available.	Lessons 1, 4

Teaching Standards

The suggested teaching strategies in all the lessons support you as you work to meet the teaching standards outlined in the *National Science Education Standards*. This module helps you plan an inquiry-based science program by providing short-term objectives for students. It also includes planning tools such as the Conceptual Flow of the Lessons chart and the Suggested Timeline for teaching the module. You can use this module to update your curriculum in response to your students' interest in this topic. The focus on active, collaborative, and inquiry-based learning in the lessons helps you support the development of student understanding and nurture a community of science learners.

The structure of the lessons in this module enables you to guide and facilitate learning. All the activities encourage and support student inquiry, promote discourse among students, and challenge students to accept and share responsibility for their learning. Using the 5E Instructional Model, combined with active, collaborative learning, allows you to respond effectively to the diversity of student backgrounds and learning styles. The module is fully annotated, with suggestions for how you can encourage and model the skills of scientific inquiry, as well as foster the curiosity, openness to new ideas and data, and skepticism that characterize successful study of science.

Assessment Standards

You can engage in ongoing assessment of your teaching and of student learning using the variety of assessment components embedded within the module's structure. The assessment tasks are authentic; they are similar to tasks that students will engage in outside the classroom or in which scientists participate. Annotations guide you to these opportunities for assessment and provide answers to questions that can help you analyze student feedback.

How Does the 5E Instructional Model Promote Active, Collaborative, Inquiry-Based Learning?

Because learning does not occur through a process of passive absorption, the lessons in this module promote active learning. Students are involved in more than listening and reading. They are developing skills, analyzing and evaluating evidence, experiencing and discussing, and talking to their peers about their own understandings. Students work collaboratively with others to solve problems and plan investigations. Many students find that they learn better when they work with others in a collaborative environment than when they work alone in a competitive environment. When all this active, collaborative learning is directed toward inquiry science, students succeed in making their own discoveries. They ask questions, observe, analyze, explain, draw conclusions, and ask new questions. These inquiry experiences include both those that involve students in direct experimentation and those in which students develop explanations through critical and logical thinking.

This view of students as active thinkers who construct their own understanding out of interactions with phenomena, the environment, and other individuals is based on the theory of **constructivism**. A constructivist view of learning recognizes that students need time to

- express their current thinking;
- interact with objects, organisms, substances, and equipment to develop a range of experiences on which to base their thinking;
- reflect on their thinking by writing and expressing themselves and comparing what

they think with what others think; and
- make connections between their learning experiences and the real world.

This module provides a built-in structure for creating a constructivist classroom: the 5E Instructional Model. This model sequences the learning experiences so that students have the opportunity to construct their understanding of a concept over time. The model takes students through five phases of learning that are easily described using five words that begin with the letter *E*: Engage, Explore, Explain, Elaborate, and Evaluate. The following paragraphs illustrate how the 5Es are implemented across the lessons in this module.

Engage

Students come to learning situations with prior knowledge. This knowledge may or may not be congruent with the concepts presented in this module. Engage lessons provide the opportunity for teachers to find out what students already know or think they know about the topic and concepts to be covered.

The Engage lesson in this module, Lesson 1: *What Is Technology?*, is designed to
- pique students' curiosity and generate interest;
- determine students' current understanding about technology;
- invite students to raise their own questions about technology;
- encourage students to compare their ideas with the ideas of others; and
- enable teachers to assess what students do or do not understand about the stated outcomes of the lesson.

Explore

In the Explore portions of the module, Lesson 1: *How Low Can You Go?* (Activity 2), Lesson 2: *Resolving Issues*, and Lesson 3: *Putting Technology to Work*, students investigate scale, resolution, and the utility of technology to solve scientific problems, including those relevant to human health. These lessons require students to make observations, evaluate and interpret data, and draw conclusions. Students
- interact with materials and ideas through classroom and Web activities;
- consider different ways to solve a problem or answer a question;
- acquire a common set of experiences with their classmates so they can compare results and ideas;
- observe, describe, record, compare, and share their ideas and experiences; and
- express their developing understanding of technology by analyzing and interpreting data and by answering questions.

Explain

The Explain lessons provide opportunities for students to connect their previous experiences and to begin to make conceptual sense of the main ideas of the module. This stage also allows for the introduction of formal language, scientific terms, and content information that might make students' previous experiences easier to describe and explain.

In the Explain lessons in this module, Lesson 1: *What Is Technology?*, Lesson 2: *Resolving Issues*, and Lesson 3: *Putting Technology to Work*, students
- explain concepts and ideas about technology (in their own words);
- listen to and compare others' explanations of their results with their own;
- become involved in student-to-student discourse in which they explain their thinking to others and debate their ideas;
- revise their ideas;
- record their ideas and current understanding;
- use labels, terminology, and formal language; and
- compare their current thinking with what they previously thought.

Elaborate

In the Elaborate lesson, Lesson 3: *Putting Technology to Work*, students apply or extend important concepts in new situations and relate their previous experiences to new ones. Students make conceptual connections between new and former experiences. In this lesson, students
- connect ideas, solve problems, and apply their understanding in a new situation;

- use scientific terms and descriptions;
- draw reasonable conclusions from evidence and data;
- add depth to their understanding of concepts and processes; and
- communicate their understanding to others.

Evaluate

The Evaluate lesson is the final stage of the instructional model, but it only provides a "snapshot" of what the students understand and how far they have come from where they began. In reality, the evaluation of students' conceptual understanding and ability to use skills begins with the Engage lesson and continues throughout each stage of the instructional model, as described in the following section. Combined with the students' written work and performance of tasks throughout the module, however, the Evaluate lesson can serve as a summative assessment of what students know and can do.

The Evaluate lesson in this module, Lesson 4: *Technology: How Much Is Enough?*, provides an opportunity for students to

- demonstrate what they understand about technology and how well they can apply their knowledge to solve a problem;
- share their current thinking with others;
- assess their own progress by comparing their current understanding with their prior knowledge; and
- ask questions that take them deeper into a concept.

To review the relationship of the 5E Instructional Model to the concepts presented in the module, see the Conceptual Flow of the Lessons chart, on page 6.

When a teacher uses the 5E Instructional Model, he or she engages in practices that are very different from those of a traditional teacher. In response, students also participate in their learning in ways that are different from those experienced in a traditional classroom. The following charts, What the Teacher Does and What the Students Do, outline these differences.

What the Teacher Does

Stage	That is *consistent* with the 5E Instructional Model	That is *inconsistent* with the 5E Instructional Model
Engage	• Piques students' curiosity and generates interest • Determines students' current understanding (prior knowledge) of a concept or idea • Invites students to express what they think • Invites students to raise their own questions	• Introduces vocabulary • Explains concepts • Provides definitions and answers • Provides closure • Discourages students' ideas and questions
Explore	• Encourages student-to-student interaction • Observes and listens to the students as they interact • Asks probing questions to help students make sense of their experiences • Provides time for students to puzzle through problems	• Provides answers • Proceeds too rapidly for students to make sense of their experiences • Provides closure • Tells the students that they are wrong • Gives information and facts that solve the problem • Leads the students step-by-step to a solution

Explain	• Encourages students to use their common experiences and data from the Engage and Explore lessons to develop explanations • Asks questions that help students express understanding and explanations • Requests justification (evidence) for students' explanations • Provides time for students to compare their ideas with those of others and perhaps to revise their thinking • Introduces terminology and alternative explanations after students express their ideas	• Neglects to solicit students' explanations • Ignores data and information students gathered from previous lessons • Dismisses students' ideas • Accepts explanations that are not supported by evidence • Introduces unrelated concepts or skills
Elaborate	• Focuses students' attention on conceptual connections between new and former experiences • Encourages students to use what they have learned to explain a new event or idea • Reinforces students' use of scientific terms and descriptions previously introduced • Asks questions that help students draw reasonable conclusions from evidence and data	• Neglects to help students connect new and former experiences • Provides definitive answers • Tells students that they are wrong • Leads students step-by-step to a solution
Evaluate	• Observes and records as students demonstrate their understanding of concept(s) and performance of skills • Provides time for students to compare their ideas with those of others and perhaps to revise their thinking • Interviews students as a means of assessing their developing understanding • Encourages students to assess their own progress	• Tests vocabulary words, terms, and isolated facts • Introduces new ideas or concepts • Creates ambiguity • Promotes open-ended discussion unrelated to the concept or skill

What the Students Do

Stage	That is *consistent* with the 5E Instructional Model	That is *inconsistent* with the 5E Instructional Model
Engage	• Become interested in and curious about the concept/topic • Express current understanding of a concept or idea • Raise questions such as, What do I already know about this? What do I want to know about this? How could I find out?	• Ask for the "right" answer • Offer the "right" answer • Insist on answers or explanations • Seek closure
Explore	• "Mess around" with materials and ideas • Conduct investigations in which they observe, describe, and record data • Try different ways to solve a problem or answer a question • Acquire a common set of experiences so they can compare results and ideas • Compare their ideas with those of others	• Let others do the thinking and exploring (passive involvement) • Work quietly with little or no interaction with others (only appropriate when exploring ideas or feelings) • Stop with one solution • Demand or seek closure
Explain	• Explain concepts and ideas in their own words • Base their explanations on evidence acquired during previous investigations • Record their ideas and current understanding • Reflect on and perhaps revise their ideas • Express their ideas using appropriate scientific language • Compare their ideas with what scientists know and understand	• Propose explanations from "thin air" with no relationship to previous experiences • Bring up irrelevant experiences and examples • Accept explanations without justification • Ignore or dismiss other plausible explanations • Propose explanations without evidence to support their ideas
Elaborate	• Make conceptual connections between new and former experiences • Use what they have learned to explain a new object, event, organism, or idea • Use scientific terms and descriptions • Draw reasonable conclusions from evidence and data • Communicate their understanding to others	• Ignore previous information or evidence • Draw conclusions from "thin air" • Use terminology inappropriately and without understanding

Evaluate	• Demonstrate what they understand about the concept(s) and how well they can implement a skill • Compare their current thinking with that of others and perhaps revise their ideas • Assess their own progress by comparing their current understanding with their prior knowledge • Ask new questions that take them deeper into a concept or topic area	• Disregard evidence or previously accepted explanations in drawing conclusions • Offer only yes-or-no answers or memorized definitions or explanations as answers • Fail to express satisfactory explanations in their own words • Introduce new, irrelevant topics

How Does the Module Support Ongoing Assessment?

Because teachers will use this module in a variety of ways and at a variety of points in the curriculum, the most appropriate mechanism for assessing student learning is one that occurs informally at various points within the four lessons, rather than something that happens more formally just once at the end of the module. Accordingly, integrated within the four lessons in the module are specific assessment components. These "embedded" assessment opportunities include one or more of the following strategies:

- performance-based activities (for example, developing graphs or participating in a discussion of health effects or social policies);
- oral presentations to the class (for example, presenting experimental results); and
- written assignments (for example, answering questions or writing about demonstrations).

These strategies allow the teacher to assess a variety of aspects of the learning process, such as students' prior knowledge and current understanding, problem-solving and critical-thinking skills, level of understanding of new information, communication skills, and ability to synthesize ideas and apply understanding to a new situation.

An assessment icon and an annotation that describes the aspect of learning that teachers can assess appear in the margin beside each step in which embedded assessment occurs.

How Can Controversial Topics Be Handled in the Classroom?

Teachers sometimes feel that the discussion of values is inappropriate in the science classroom or that it detracts from the learning of "real" science. The lessons in this module, however, are based on the conviction that there is much to be gained by involving students in analyzing issues of science, technology, and society. Society expects all citizens to participate in the democratic process, and our educational system must provide opportunities for students to learn to deal with contentious issues with civility, objectivity, and fairness. Likewise, students need to learn that science intersects with life in many ways.

In this module, students have a variety of opportunities to discuss, interpret, and evaluate basic science and health issues, some in the light of values and ethics. As students encounter issues about which they feel strongly, some discussions might become controversial. How much controversy develops will depend on many factors, such as how similar the students are with respect to socioeconomic status, perspectives, value systems, and religious preferences. In addition, the language and attitude of the teacher factor into the flow of ideas and the quality of exchange among the students.

The following guidelines may help you facilitate discussions that balance factual information with feelings.

- Remain neutral. Neutrality may be the single most important characteristic of a successful discussion facilitator.
- Encourage students to discover as much

information about the issue as possible.

- Keep the discussion relevant and moving forward by questioning or posing appropriate problems or hypothetical situations. Encourage everyone to contribute, but do not force reluctant students to enter the discussion.
- Emphasize that everyone must be open to hearing and considering diverse views.
- Use unbiased questioning to help the students critically examine all views presented.
- Allow for the discussion of all feelings and opinions.
- Avoid seeking consensus on all issues. The multifaceted issues that the students discuss result in the presentation of divergent views, and students should learn that this is acceptable.
- Acknowledge all contributions in the same evenhanded manner. If a student seems to be saying something for its shock value, see whether other students recognize the inappropriate comment and invite them to respond.
- Create a sense of freedom in the classroom. Remind students, however, that freedom implies the responsibility to exercise that freedom in ways that generate positive results for all.
- Insist upon a nonhostile environment in the classroom. Remind students to respond to ideas instead of to the individuals presenting those ideas.
- Respect silence. Reflective discussions often are slow. If a teacher breaks the silence, students may allow the teacher to dominate the discussion.
- At the end of the discussion, ask the students to summarize the points that they and their classmates have made. Respect students regardless of their opinion about any controversial issue.

Using the Student Lessons

The heart of this module is a set of four classroom lessons that allow students to discover important concepts related to technology and its role in developing our understanding of cellular and molecular biology. To review these concepts in detail, refer to the Conceptual Flow of the Lessons chart, on page 6.

Format of the Lessons

As you review the lessons, you will find that all contain common major features.

At a Glance offers a convenient summary of the lesson.

- **Overview** provides a short summary of student activities.
- **Major Concepts** presents the central ideas that the lesson is designed to convey.
- **Objectives** lists specific understandings or abilities students should derive from completing the lesson.
- **Teacher Background** specifies which portions of the background section, *Information about Using Technology to Study Cellular and Molecular Biology*, relate directly to the lesson. This reading material provides the science content that supports the key concepts covered in the lesson. The information provided is not intended to form the basis of lectures to students nor is it intended as a direct resource for students. Rather, it enhances your understanding of the content so that you can facilitate class discussions, answer student questions, and provide additional examples.

In Advance provides instructions for collecting and preparing materials required to complete the activities in the lesson.

- **Web-Based Activities** tells you which of the lesson's activities use the *Using Technology to Study Cellular and Molecular Biology* Web site as the basis for instruction.
- **Photocopies** lists the paper copies and transparencies that need to be made from masters that are provided after Lesson 4, at the end of the module.
- **Materials** lists all items other than photocopies needed for the activities in the lesson.
- **Preparation** outlines what you need to do to be ready to teach the activities in the lesson.

Procedure provides a step-by-step approach for conducting each activity in the classroom. It includes implementation suggestions and answers to discussion questions.

Within the Procedure section, annotations provide additional commentary.

- **Tip from the field test** details suggestions from field-test teachers for teaching strategies, class management, and module implementation.
- **Assessment** provides strategies for gauging student progress throughout the module, and is identified by an assessment icon (see page 18).
- **Icons** identify specific annotations:

identifies teaching strategies that address specific science content standards as defined by the *National Science Education Standards*.

identifies when to use the Web site as part of the teaching strategy. Instructions in the Procedure section tell you how to access the Web

site and the relevant activity. Information about using the Web site can be found in *Using the Web Site* (see page 19). A print-based alternative to each Web activity is provided for classrooms in which Internet access is not available.

identifies a print-based alternative to a Web-based activity to be used when computers are not available.

identifies when assessment is embedded in the module's structure. An annotation suggests strategies for assessment.

Lesson Organizer provides a brief summary of the lesson. It outlines procedural steps for each activity and includes icons that denote where in each activity masters, transparencies, and the Web site are used. The lesson organizer is intended to be used only after you become familiar with the lesson materials. It can be a handy resource during lesson preparation as well as during classroom instruction.

Masters to be photocopied are found after Lesson 4, at the end of the module.

Timeline for the Module

The timeline below outlines the optimal plan for completing the four lessons in this module. The plan assumes you will teach the activities on consecutive days. If your class requires more time for discussing issues raised in this module or for completing activities, adjust your timeline accordingly.

Suggested Timeline

Timeline	Activity
3 weeks ahead	Reserve computers Check performance of Web site
1 week ahead	Make photocopies and transparencies Gather materials
Day 1 Monday	**Lesson 1** Activity 1: *Technology—What's It All About?* Activity 2: *Searching for Scale*
Day 2 Tuesday	**Lesson 2** Activity 1: *Probing for Answers* Activity 2: *More than Meets the Eye*
Day 3 Wednesday	**Lesson 3** Activity 1: *Putting Technology to Work*; Part 1, some of Part 2
Day 4 Thursday	Part 2 (conclude), Part 3, and Part 4 (print version only)
Day 5 Friday	**Lesson 4** Activity 1: *Time Travel* Activity 2: *Is That All There Is?*
Day 6 Monday	Activity 2: *Is That All There Is?* (conclude)

Using the Web Site

The *Using Technology to Study Cellular and Molecular Biology* Web site is a wonderful tool that can engage student interest in learning, enhance the student's learning experience, and orchestrate and individualize instruction. The Web site features simulations that articulate with two of this unit's lessons. To access the Web site, type the following URL into your browser: *http://science.education.nih.gov/supplements/technology/student*. Click on the link to a specific lesson under *Web Portion of Student Activities*. If you do not have computer or Internet access, you can use the print-based alternative provided for each Web activity. Text pertaining only to Web-based activities is lightly shaded.

Hardware/Software Requirements

The Web site can be accessed from Apple Macintosh and IBM-compatible personal computers. Links to download the Macromedia Flash plug-in are provided on the Web site's Getting Started page. *This plug-in is required for the activities to function properly*. The recommended hardware and software requirements for using the Web site are listed in table below. Although your computer configuration may differ from those listed, the Web site may still be functional on your computer. The most important items in this list are current browsers and plug-ins.

Downloading and Installing Macromedia Flash Player

To experience full functionality of the Web site, Macromedia Flash Player, version 6.0 or higher, must be downloaded and installed on the hard drive of each computer that will be used to access the site. The procedure for downloading and installing Macromedia Flash Player is outlined below.

Recommended Hardware/Software Requirements for Using the Web Site*

CPU/Processor (PC Intel, Mac)	Pentium III, 600 MHz; or Mac G4
Operating system (DOS/Windows, Mac OS)	Windows 2000 or higher; or Mac OS 9 or newer
System memory (RAM)	256 MB
Screen setting	1024 × 768 pixels, 32 bit color
Browser	Netscape Communicator 7.1 or Microsoft Internet Explorer 6
Browser settings	JavaScript Enabled
Free hard drive space	10 MB
Connection speed	56 kbps modem or high-speed Internet connection
Plug-ins, installed for your Web browser	Macromedia Flash Plug-In, version 6 or better; or Apple QuickTime Plug-In, version 6 or better
Audio	Sound card with speakers

*For users of screen-reader software, a multichannel sound card such as Sound Blaster® Live!™ is recommended.

- Open a Web browser.
- Access the main page of the Web site at *http://science.education.nih.gov/supplements/technology/teacher*.
- Click on the "Getting Started" section.
- Click on the link to "Macromedia Flash." This will bring up the Macromedia Flash Player Download Center Web site.
- The Download Center Web site should present you with the option of installing the latest version (highest number) of Macromedia Flash Player. As of August 2004, this should be at least version 7.0.
- Click on the button marked "Install Now," or "Download Now." Clicking this button will allow Macromedia's Web site to download and install Flash Player on your computer's hard drive. If you are using Internet Explorer, the installation will happen automatically after clicking the "Install Now" button. If you are using Netscape, you will have to download and run the installation file. Follow the on-screen instructions provided.
- Your Web browser may present you with a Security Dialog Box asking if you would like to install and run Macromedia Flash Player. Click "Yes."
- After a minute or so, you should once again see the Macromedia Download Center Web page on your browser. There will be a box toward the top of the page containing clickable text. The appearance of this box in your browser window indicates that you have successfully downloaded and installed Macromedia Flash Player.

Getting the Most out of the Web Site

Before you use the Web site, or any other piece of instructional software in your classroom, it may be valuable to identify some of the benefits you can expect the software to provide. Well-designed instructional multimedia software can

- motivate students by helping them enjoy learning and want to learn more because it enlivens content that students otherwise might find uninteresting;
- offer unique instructional capabilities that allow students to explore topics in greater depth and in ways that are closer to actual real-life experience than print-based resources can offer;
- provide teachers with support for experimenting with new instructional approaches that allow students to work independently or in small teams and that give teachers increased credibility among today's technology-literate students; and
- increase teachers' productivity by helping them with assessment, record keeping, and classroom planning and management.

The ideal use of the Web site requires one computer for each student team. However, if you have only one computer available, you can still use the Web site. For example, you can use a projection system to display the monitor image for the whole class to see. Giving selected students in the class the opportunity to manipulate the Web activities in response to suggestions from the class can give students some of the same autonomy in their learning that they would gain from working in small teams. Alternatively, you can rotate student teams through the single computer station.

Collaborative Groups

Many of the activities in the lessons are designed to be completed by teams of students working together. Although individual students working alone can complete these activities, this strategy will not stimulate the types of student-student interactions that are part of active, collaborative, inquiry-based learning. Therefore, we recommend that you organize collaborative teams of two to four students each, depending on the number of computers available. Students in teams larger than this will have difficulty organizing student-computer interactions equitably. This can lead to one or two students' assuming the primary responsibility for the computer-based work. Although this type of arrangement can be efficient, it means that some students will not have the opportunity to experience the in-depth discovery and analysis that the Web site was designed to stimulate. Team members not involved directly may become bored or disinterested.

We recommend that you keep students in the same collaborative teams for all the activities in the lessons. This will allow each team to develop a shared experience with the Web site and with the ideas and issues that the activities present. A shared experience will also enhance your students' perceptions of the lesson as a conceptual whole.

If your student-to-computer ratio is greater than four to one, you will need to change the way you teach the module from the instructions in the lessons. For example, if you have only one computer available, you may want students to complete the Web-based work over an extended time period. You can do this several ways. The most practical way is to use your computer as a center along with several other centers at which students complete other activities. In this approach, students rotate through the computer center, eventually completing the Web-based work you have assigned.

A second way to structure the lessons if you have only one computer available is to use a projection system to display the desktop screen for the whole class to view. Giving selected students in the class the opportunity to manipulate the Web activities in response to suggestions from the class can give students some of the same autonomy in their learning they would have gained from working in small teams.

Web Activities for Students with Disabilities

The Office of Science Education (OSE) is committed to providing access to the Curriculum Supplement Series for individuals with disabilities, including members of the public and federal employees. To meet this commitment, we will comply with the requirements of Section 508 of the Rehabilitation Act. Section 508 requires that individuals with disabilities who are members of the public seeking these materials will have access to and use of information and data that are comparable to those provided to members of the public who are not individuals with disabilities. The online versions of this series have been prepared to comply with Section 508.

If you use assistive technology (such as a Braille reader or a screen reader) and the format of any material on our Web sites interferes with your ability to access the information, please let us know. To enable us to respond in a manner most helpful to you, please indicate the nature of your accessibility problem, the format in which you would like to receive the material, the Web address of the requested material, and your contact information.

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Using Technology to Study Cellular and Molecular Biology 508-Compliant Web Activities

Lesson	For Students with Hearing Impairment	For Students with Sight Impairment
Lesson 2, both activities	No special considerations are required.	There is no equivalent alternative to these activities for students with sight impairments. Students should be involved in the group discussions of these activities and be asked for their perspective. Supervision is recommended.
Lesson 3, Parts 1 and 3	No special considerations are required.	Students using screen-magnification or screen-reading software can choose an alternate, text-based version of the activity. The content of the alternate activity is equivalent to the original's, but it's in a text format. The activity is based on the print version of the lesson. Images within the reference manual are kept to a minimum. The print version of the activity should be kept handy for reference. **Note:** Students using a screen magnifier may prefer the original version of the activity. When the activity loads, students press a button to proceed to the original version or the screen-reader-friendly version of the activity. Use the "Teacher Administration" link to generate login codes for your students. You will need one code for each student using this version of the activity. You may request up to 100 codes at one time. The "Progress Map" at the bottom of each page keeps track of each student's progress. If a student closes the activity and returns later, he will resume where he left off. The last page of the activity provides a summary of all the student's answers. To edit their responses, students can use the Progress Map to return to any page they have completed. The computer the students use must be linked to a printer. Supervision is recommended.
Lesson 3, Part 2	No special considerations are required.	This activity has been incorporated into the print version of Lesson 3.

Information about Using Technology to Study Cellular and Molecular Biology

1 Introduction

For society to gain the most from **technology**, the public must be able to understand scientific issues and consider them rationally. This point is made in the *National Science Education Standards*: "Because molecular biology will continue into the 21st century as a major frontier of science, students should understand the chemical basis of life, not only for its own sake, but because of the need to take informed positions on some of the practical and ethical implications of humankind's capacity to tinker with the fundamental nature of life."

A molecular genetic perspective affords teachers an opportunity to help integrate many of biology's subdisciplines. This integrative process began with the advent of recombinant-DNA technology and is now being propelled by the new areas of **bioinformatics** and genomic biology. According to the *National Science Education Standards*, molecular and evolutionary biology are among the "small number of general principles that can serve as the basis for teachers and students to develop further understanding of biology." A similar point is made in a medical context by the new *Standards for Technology Literacy*, which recognizes that "the use of technology has made numerous contributions to medicine over the years. Scientific and technological breakthroughs are at the core of most diagnostic and treatment practices."[12]

When teachers try to relate advances in technology to biology, they may be frustrated by the fact that there is a lag, measured in years, between scientific advance and its inclusion in the curriculum. For example, the polymerase chain reaction (PCR) was introduced to the scientific community in 1985. Biology teachers became aware of the technique through stories in the media and wanted to learn more about it. It was not until 1990, however, when PCR inventor Kary Mullis published an article about the technique in *Scientific American*, that teachers found an accessible treatment of this important technology. It took another few years for PCR to be mentioned in most high school biology textbooks. This curriculum supplement, *Using Technology to Study Cellular and Molecular Biology*, will help short-circuit the usually lengthy process by which technology makes its way to the classroom.

2 Major Preconceptions

Preconception 1. Study in one field proceeds without contributions from, or connections to, other fields.

This belief occurs, in part, because scientific disciplines are treated as isolated subjects in most schools. Most science educators, however, recognize the many connections among biology, chemistry, and physics, and understand the need for an integrated approach to science teaching. For example, molecular biology is a hybrid discipline, drawing upon concepts and techniques from physics, chemistry, and biology. This hybrid nature explains in part why high school students may find the study of molecular biology challenging. They are confronted by a science that is abstract and seems far removed from classical biology. Moreover, many students are introduced to the subject at a point in their education where they have yet to take a formal course in either chemistry or physics. Without this scientific foundation, they are ill-prepared to undertake the study of life at its most fundamental level.

Preconception 2. Most of what students are exposed to in science classes is about science, not technology.
Additionally, technology is about computers rather than about a way of adapting or a process for solving a problem. It is important for students to learn that each of the technologies covered in this supplement is a tool applied to a specific task. The supplement will help students recognize the type of scientific information that can be obtained from various techniques and gain an appreciation for and an understanding of the role technology has played in advancing our understanding of biological systems.

Preconception 3. Students are likely to have preconceptions about the contributions that a range of technologies has made to science and medicine, that is, about the problem-solving capacity of technology.
For example, students have probably looked at a specimen with a light microscope, and they have seen photomicrographs in textbooks. However, students have limited experience evaluating the information conveyed at the microscopic level and placing it in the proper context. Consequently, it will be important in this supplement to help students gain a perspective of the relative sizes of cellular and molecular structures. The concepts of **resolution** and **scale** can help students appreciate that structures invisible to the unaided eye, such as mitochondria, ribosomes, viruses, and protein molecules, have vastly different sizes and require different technologies for study. It is important that this supplement help students understand the need to obtain information from more than one technique to solve a problem.

The concepts of resolution and scale can help students appreciate that structures invisible to the unaided eye, such as mitochondria, ribosomes, viruses, and protein molecules, have vastly different sizes and require different technologies for study.

Preconception 4. Structure and function are independent and unrelated concepts.
This supplement can build a foundation to address this preconception and to help students understand the interdependence of structure and function. With this supplement, students will explore concepts to help them understand that technologies provide scientists with essential information about structure. The relationship between structure and function may be easier for students to understand at a macroscopic level, and students may struggle to understand this relationship at the abstract level of molecules. Inquiry-based activities will allow students to learn what structure is and at how many levels structure can be defined. Through these activities, students will learn how developing structural information at various tiers provides increasingly greater information about function. Structure-function relationships are critical to understanding normal cellular processes, as well as those associated with disease. Such intimate knowledge of biomolecules promises to expand the range of drug targets, shift the discovery effort from direct screening programs to rational **target-based drug design**, and usher in a new era of personalized medicine. One of the activities that follows—in Lesson 3, *Putting Technology to Work*—gives students insight into these scientific developments.

3 Scale and Resolution

3.1 Scale

How big is "big"? How small is "small"? It depends, of course, on one's point of reference. An insect such as a bee (about 12 mm in length) is very small compared with a human (perhaps 1.7 to 2 meters in height). However, a bee is very large compared with one of the pollen grains it gathers (about 30 µm, or 0.03 mm, in diameter). While it may be easy to discern the relative sizes of some objects, such as those we can see with the naked eye, it is far more difficult to imagine the size of things that are very large or very small. For instance, how large is a lightyear? Can we conceive of the difference between 10 lightyears and 100 lightyears? What is the distance across a cell? A virus? A protein

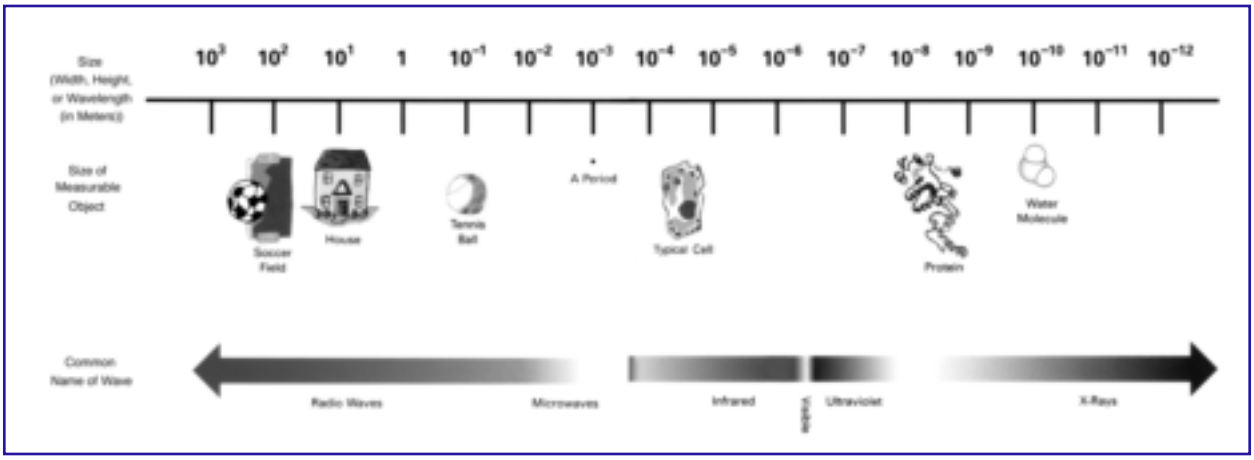

Figure 1. Size of some familiar objects and energy waves on a logarithmic scale.

molecule? How much larger are these than the distance between two adjacent carbon atoms in a sugar molecule? Importantly, where do we humans fit into the picture?

To understand the continuum from small to large, we need a way to represent the relationship between the actual size of an object (for example, its length or mass) and how that size is characterized either numerically or visually. We need a scale, a series of ascending and descending steps to assess the relative or absolute size of some property of an object. Scales can have upper and lower values, as required. They may be linear, or, when the distance between upper and lower values is very large, they may be logarithmic. Figure 1 presents the size of some familiar objects and energy waves on a logarithmic scale.

Without some notion of scale, a water molecule might appear to be as large as a house if both are drawn to occupy the same physical space on a piece of paper.

3.2 Resolution

In cellular and molecular biology, we are interested in resolving structural details of organs and tissues at the cellular level, of the intricacies that form the intracellular environment, of the molecules that make up living systems, and of molecular interactions. We are interested in understanding how living systems function. How do muscles contract? How do enzyme reactions occur? How are metabolic pathways regulated? How are molecules transported from one site to another? How do antibodies recognize antigens? We want answers to so many questions related to how living systems function that require us to understand molecular structure first. Why? A molecule's function is determined by and is dependent on its structure. So, how do we get information about the structure of biological molecules? Consider the following:

As we look down a street in a residential neighborhood, we note individual houses because we are capable of distinguishing the space between the houses. We accomplish this feat using our visual system to detect visible light. In other words, visible light is the **probe** we use to resolve these discrete structures. In a general sense, we can think of resolving power as a measure of the ability of a system to form separate and distinct images of two objects of a given angular separation. This relationship is derived from the laws of optics. What does this mean to the study of cellular and molecular biology? In the laws of optics, two objects can be resolved if they are illuminated with radiation of wavelength that is not larger than the distance separating the objects. Visible light has a **wavelength** of 4,000 to 7,000 **angstroms**

(Å; 1 Å = 10^{-8} cm = 10^{-10} m), or 4 to 7 × 10^{-7} m, and is a great probe for viewing a portion of our world. We can resolve much with the naked eye and even more, such as cells and cell organelles, with a light microscope. However, its wavelength makes it unusable as a probe for resolving much smaller objects, such as molecules and atoms. Other probes with smaller wavelengths are required for this task.

4 Major Techniques in the Study of Cellular and Molecular Biology

There is a reciprocal relationship between technology and the process of science. Improvements in technology enable scientists to investigate questions that were previously difficult, or even impossible, to address. At the same time, scientific curiosity often provides the impetus for refining an existing technology or developing a new one. This section provides a brief survey of some technologies important to the study of cellular and molecular biology. It presents a sampling of current research in cellular and molecular biology, showing that techniques that have been around for decades continue to be refined and put to new uses, sometimes in combination with other techniques.

4.1 Microscopy

The development of the microscope allowed us to extend our view to things not visible to the naked eye. Consider what our view of biological systems would be if we had no knowledge of cells and cell structure. Figure 2 depicts the development of three major types of microscopy over time.

The line for each type of microscopy shows how improvements in technology have

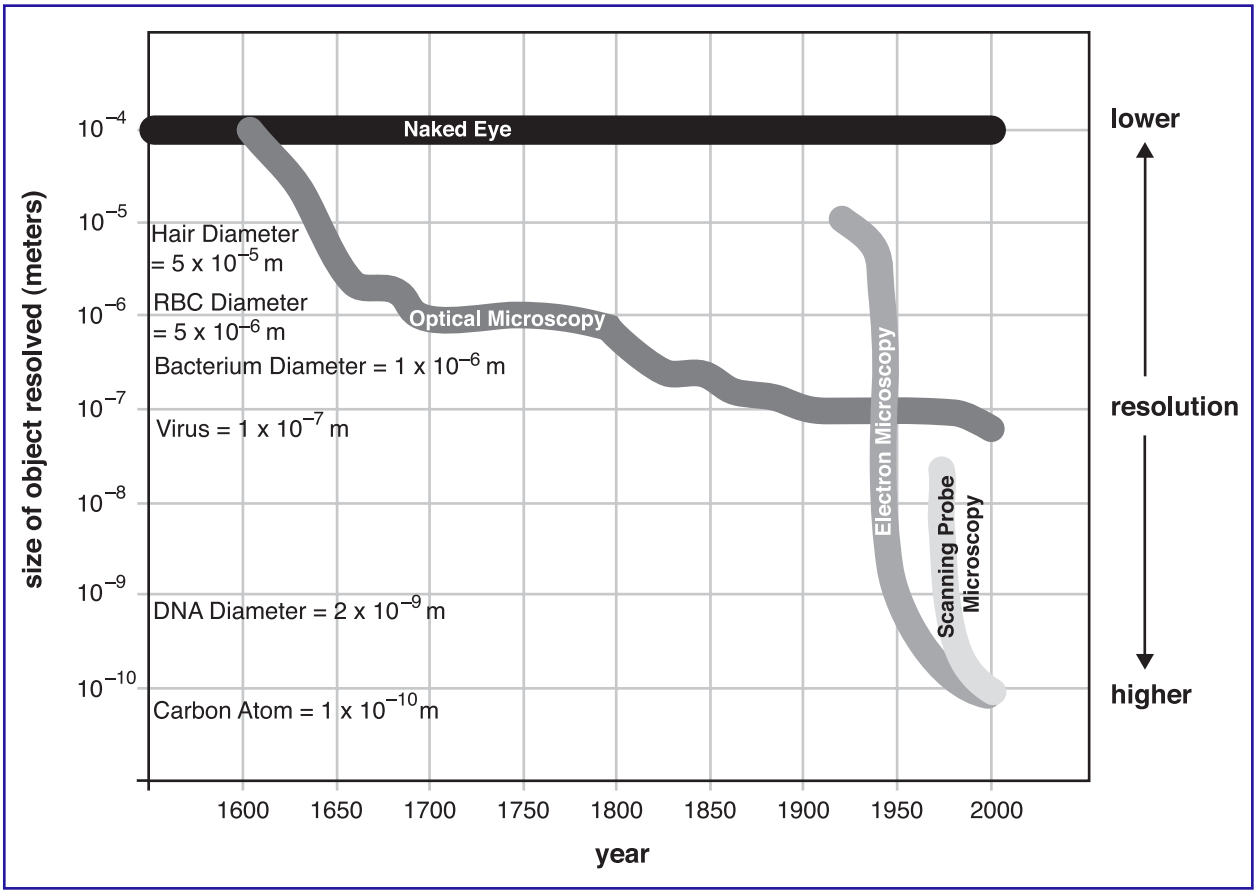

Figure 2. Development and resolution of three major types of microscopy over time.

increased the resolution available with each technique. Higher resolution means being able to see smaller objects.

Figure 3. Optical microscope.

Optical microscopy. The first microscopes were optical microscopes, which used glass lenses to focus and magnify light. The first optical microscope was constructed around 1695 by Hans and Sacharias Janssen, but it wasn't until 60 to 80 years later that major discoveries were made with this technology. By viewing capillaries under a microscope in 1660, Marcello Malpighi proved the controversial theory that blood circulates in a circular motion from the heart around the body and back to the heart. Also about this time, Robert Hooke is credited with discovering the cell, the basic unit of life. Antonio van Leeuwenhoek improved the lenses used in microscopes, allowing an increase in maximum magnification from 50× to 200×. Because of this, Leeuwenhoek was the first scientist to view bacteria, protozoa, and sperm cells. There were additional improvements to optical microscopy over the next 200 to 300 years, which ultimately allowed optical microscopes to distinguish objects as small as 200 **nanometers** (nm; 2×10^{-7} m). This resolution is a physical limit dictated by the wavelength of light (see section 3.2).

Electron microscopy. The first electron microscope was built in 1933 by Ernst Ruska, who was awarded the 1986 Nobel Prize in Physics for his achievements in electron optics. To break the 200-nm optical-resolution barrier, Ruska used accelerated electrons instead of light and magnetic coils instead of glass lenses to make an image. Electrons have a wavelength that is 10^4 to 10^5 times smaller than the wavelength of light. This allows electron microscopes to resolve objects that are 10^3 times smaller than the smallest resolvable object in a light microscope.

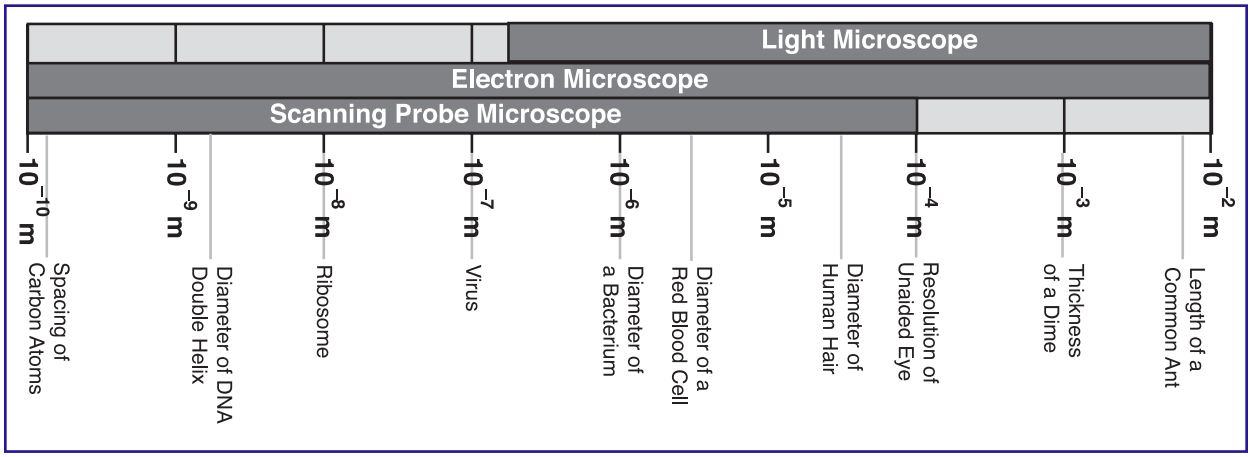

Figure 4. Resolution of three major types of microscopes.

Interestingly, although the design and physical appearance of electron microscopes have changed over the years, the essential characteristics remain the same. All electron microscopes require a high vacuum in which to form an electron beam and high voltage to control this beam. Electromagnetic lenses then focus the electron beam onto the specimen and viewing screen.

Figure 5 shows a typical transmission electron microscope (TEM). Note the much larger physical size compared with a standard light microscope, which fits comfortably on a laboratory bench. TEMs are patterned after standard transmission light microscopes and yield similar information about the size, shape, and arrangement of particles that make up a specimen, albeit at much higher resolution and with a magnification range of about 1,000× to 300,000×.

Figure 5. A typical transmission electron microscope (TEM).

The state-of-the-art TEM is the high-resolution TEM (Figure 6), which can magnify a sample up to 50,000,000 times and provide a resolution of 0.1 nm. It can produce information that complements data obtained from **X-ray** techniques (see section 4.2).

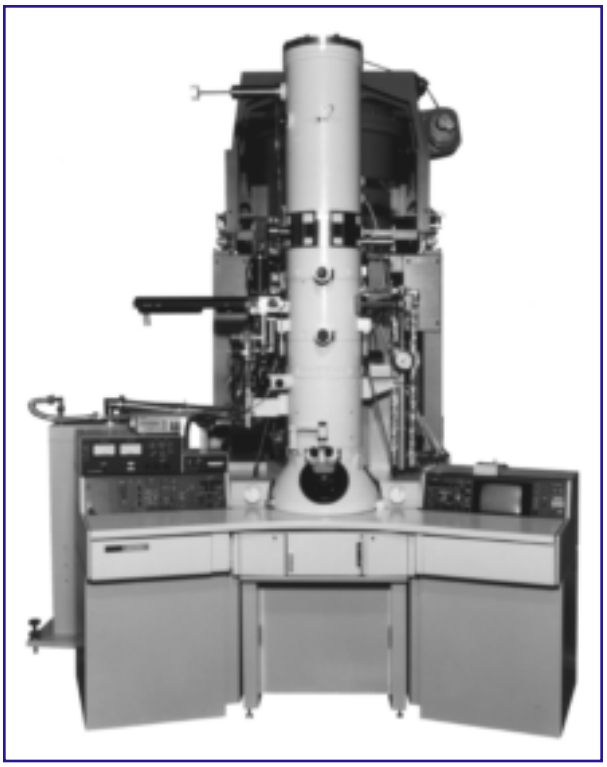

Figure 6. High-resolution TEM.

Figure 7. Scanning electron microscope.

In addition to the TEM, the other most common electron microscope is the scanning electron microscope (SEM; Figure 7). The SEM provides information about the surface features of an object. We learn about an object's appearance, texture, and detectable features to within a resolution of several nanometers. Interestingly, we do not learn this information by viewing biological specimens directly. Biological specimens have low contrast and are difficult to see in the SEM. Consequently, high-contrast heavy atoms, such as osmium, are used to stain specimens and provide an indirect image of the underlying biological structures.

Resolution can be improved by modifications of the sample-preparation procedure. In a technique called cryo-electron microscopy (cryo-EM), specimens are rapidly frozen without formation of ice crystals that can distort the specimen's structure. It is then possible to construct two- and three-dimensional models of the sample by using a computer program that averages many electron **micrographs** taken from different angles. When the technique was first applied to the structure of the ribosome in 1991, the resolution was just 45 Å. Still, it was possible to see the two ribosome subunits and the triangular space between them. In recent years, scientists have used cryo-EM techniques to image the ribosome to 4 Å.[6–8] Studies with these techniques have revealed the surface topography of the ribosome for the first time and helped crystallographers interpret the ribosome's diffraction patterns.

Other microscopic techniques. Despite the long history of light microscopy, it is still being improved. For example, a new way to image living cells without disturbing their biochemistry has been developed. Called coherent anti-Stokes Raman scattering, the technique directs two **laser** beams into the cell. The frequencies of the lasers differ by exactly the frequency at which a particular chemical bond in the cell vibrates. The lasers cause the chemical bond to vibrate and emit its own characteristic optical signal. The lasers can focus on tiny volumes and, by moving through the cell interior, can create a chemical map of the cell. One disadvantage of the technique is that it takes many minutes to produce an image, which limits its ability to visualize rapid changes within the cell.

Another technique, called Fourier transform infrared microspectroscopy (FTIR) combines microscopy with **spectroscopy** to provide chemical information about the sample being visualized. Samples can be analyzed wet or dry, in air, at room temperature, and at normal pressure. FTIR is limited for analysis of living specimens because samples must be very thin. It has proven useful in studies of pathogenesis, however. Biochemical studies of disease often fail to detect chemical compounds associated with **pathology** because the chemicals are diluted during their analysis. FTIR can be used to pinpoint areas of disease and identify compounds in individual cells, providing insights into disease progression. The technique is currently being developed for objective evaluations of pap smears.

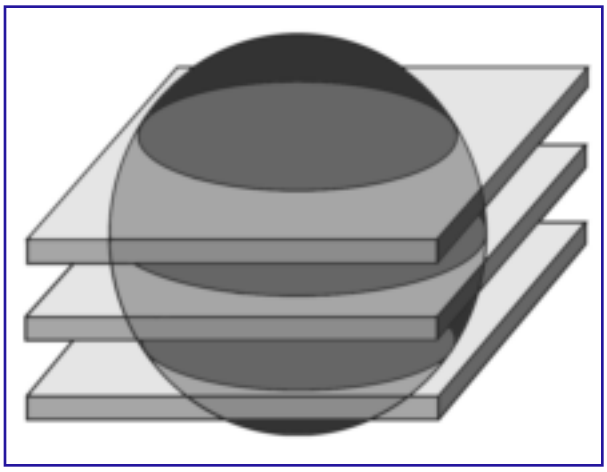

Figure 8. Laser confocal microscopes produce optical sections of biological specimens one plane at a time.

Laser confocal microscopy is a valuable tool for obtaining high-resolution images and three-dimensional reconstructions of biological specimens. This technique's major value is its ability to produce optical sections of a biological

specimen that contain information from only one focal plane. By moving the focal plane of the microscope step by step through the thickness of a specimen, a series of optical sections can be obtained. The source of light for this technique is a laser, because it can produce very high intensities. The biological specimens are stained with a fluorescent probe to make a specific structure or structures visible in the presence of the laser light.

Figure 9. Laser confocal microscope.

Confocal microscopes are not large instruments. They consist of a microscope containing a confocal attachment. In the example in Figure 9, the confocal attachment is mounted on top of the upright microscope. It contains the complicated optics package. Also necessary are a large box containing electronics, a laser, and a computer for collecting and analyzing data.

Laser confocal microscopy is being used now to study the spatial and temporal organization of the DNA-transcription apparatus. Three-dimensional reconstructions suggest that splicing factors are stored in specific areas of the nucleus. When DNA templates are introduced, these factors are recruited to sites of transcription in an intron-dependent fashion. The movement of proteins within the nucleus is also being studied using confocal microscopy.[20]

Research indicates that proteins move rapidly throughout the nucleus in an energy-independent manner. Studies such as these are helping scientists understand nuclear architecture and how nuclear processes are organized in the cell.

While electron microscopes require that samples be carefully prepared and examined in a vacuum, a new family of microscopes can achieve electron microscope resolution in air or even liquid, and they require much less sample preparation. They have even been used to study living cells. These are called scanning probe microscopes (SPMs). These instruments use a microscopic needle-like probe (3 to 50 nm at the tip) that is scanned back and forth across a surface. A three-dimensional image is constructed from the recorded interactions between the probe and the atoms in the sample. The SPM has the ability to operate on a scale from micrometers to nanometers. It can magnify an object up to 10,000,000 times. In the laboratory under ideal conditions, the SPM can be used to look at individual atoms. Furthermore, SPMs can measure properties that other microscopes cannot, such as thermal properties, friction, hardness, magnetic properties, and extent of chemical binding.

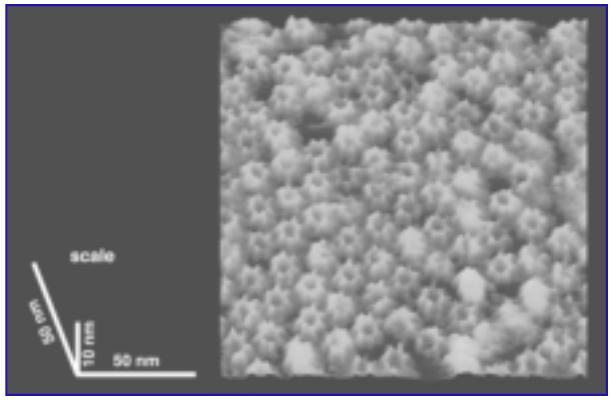

Figure 10. Molecules of the protein GroEL viewed with a scanning probe microscope (SPM). (Reprinted here with permission from Zhifeng Shao, University of Virginia. Posted at http://www.people.virginia.edu/~zs9q/zsfig/random.html.*)*

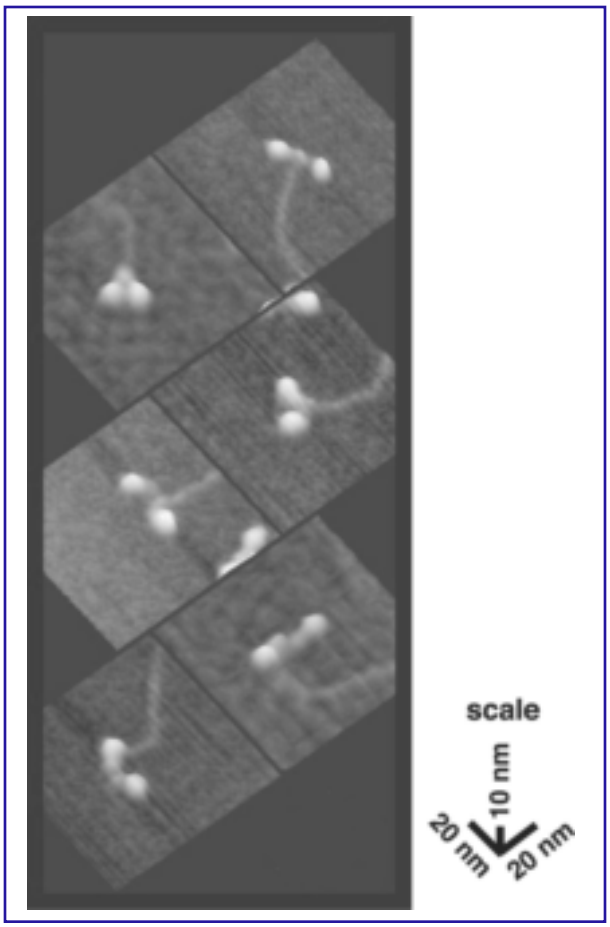

Figure 11. Myosin molecules viewed with an SPM. (Reprinted here with permission from Zhifeng Shao, University of Virginia. Posted at http://www.people.virginia.edu/~zs9q/zsfig/myosin.html.*)*

4.2 X-ray crystallography

X-ray crystallography of proteins is a perfect example of the multidisciplinary approach to technology development, since it is a combination of chemistry, physics, and biology. It was designed to determine protein structure and, in so doing, provide some information about how proteins actually function in cells. This technology, like the microscopic techniques described above, continues to evolve. While it provides detailed information about protein structure, X-ray crystallography is also being used to design better medicines for treating serious diseases.

Resolving the structure of biomolecules requires visualizing individual atoms, which are only 1 to 3 Å apart when joined to form molecules. Therefore, resolving carbon, oxygen, and nitrogen atoms requires a probe with a wavelength of less than 2 Å. Light, with a wavelength of 4,000 to 7,000 Å, cannot be used for this task. However, the wavelengths of X-rays (like electrons) are short enough that the X-rays are scattered by the electron clouds of molecules and can be used to reveal the shape of a molecule. Furthermore, X-ray techniques have some advantages over electron microscopy for determining the structure of biomolecules, such as proteins. For instance, the electron beam damages its target after a short exposure because it is powerful enough to break chemical bonds. Electron microscopy is limited to resolving biomolecules to no greater than about 7 Å, whereas X-ray crystallography can be used to resolve biomolecular structures to greater than 1 Å in some cases.

In X-ray crystallography, X-rays, with wavelengths of the same order of magnitude as the spacing between atoms, are directed through a crystal of the substance under study (Figure 12). The X-rays are bent (or **diffracted**) by the electrons surrounding the atoms in the crystal. Each diffracted X-ray is represented as a spot, whether recorded on film or electronically by a detector.

A single molecule will not produce a detectable diffraction pattern, so crystals containing many millions of identical molecules in a regular pattern are used to amplify the signal. After measuring the positions and intensities of the diffraction spots, these data can be used to calculate an electron density map. There are thousands of spots to analyze, so sophisticated computer programs and high-speed computers are needed to convert the patterns of different intensity spots into electron density maps. The maps display contour lines of electron density, thus producing an image of the electron clouds of the molecule being studied. Because electrons surround atoms more or less uniformly,

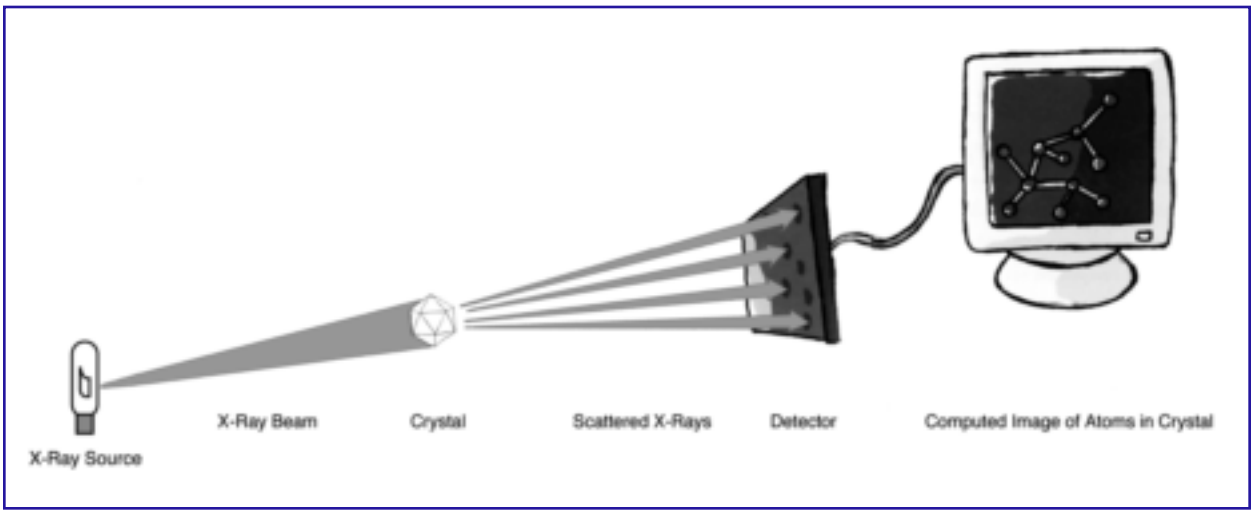

Figure 12. The X-ray crystallography process.

it is possible to determine where atoms are located by looking at these maps. By rotating the crystal and generating an electron density map for each angle of rotation, it is possible to produce a three-dimensional model of the molecule. If the amino acid sequence of a protein is known, an accurate model of the protein can be generated by fitting the atoms of the known sequence into the electron density map.

Figure 13 shows a typical diffraction pattern for a single orientation of a protein crystal through which an X-ray beam has been passed. Note the different positions and intensities of the spots, which mark the locations where scattered X-rays have struck the detector. The image is divided into quadrants because the detector was composed of four separate, adjacent modules. The white circle to the right of center with the white line extending to the left is a shadow resulting from a "beamstop." The beamstop is a small piece of lead mounted on a metal arm. It prevents the intense beam of unscattered X-rays from impinging on and damaging the detector.

Figure 14 shows a three-dimensional model of a protein that was crystallized and then analyzed by X-ray crystallography.

Equipment used in X-ray crystallography continues to undergo development and refinement. One of the most striking advancements has been the use of **synchrotron** X-rays, which are produced by the bending of particle beams generated by large accelerators. In a synchrotron, charged particles, such as electrons or positrons, are orbited around a path nearly a mile in circumference, which must be maintained in a vacuum. Understandably, synchrotrons are quite expensive to build and to maintain, and

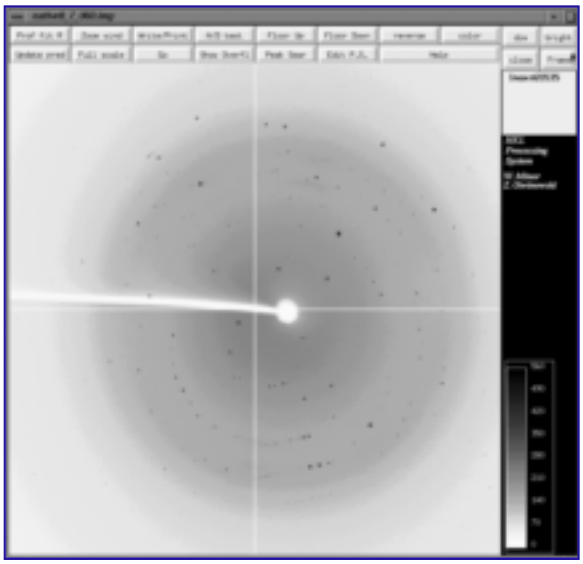

Figure 13. A typical X-ray–diffraction pattern for a single orientation of a protein crystal through which an X-ray beam has been passed.

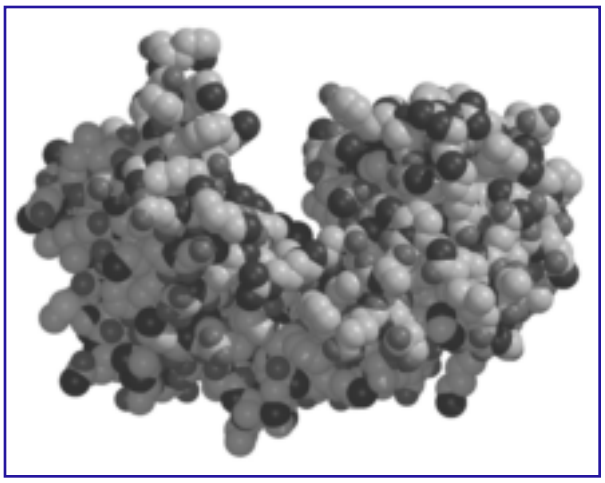

Figure 14. Three-dimensional structure of the DNA-repair protein MutY as determined by X-ray crystallography. Graphic was produced from information available at http://www.rcsb.org/pdb/.

there are fewer than 20 in the world. Because synchrotron X-ray beams are many orders of magnitude brighter than the usual laboratory X-ray sources, data for single crystal orientations can be collected with exposures of a minute or less, rather than exposures of several minutes to an hour.

The completion of the Human Genome Project has provided the foundation for explosive growth in structural biology. Technological advances in X-ray crystallography have greatly reduced the time and effort required to solve structures. In addition to synchrotron X-rays, advances include faster X-ray detectors, improved computational methods for processing data, and robotics for growing and handling crystals. Structure determinations that used to involve a 20-person, yearlong effort now constitute a single chapter in a graduate student's thesis. The Protein Structure Initiative, reminiscent of the Human Genome Project, aims to produce the three-dimensional structures for the estimated 1,000 to 5,000 distinct spatial arrangements assumed by polypeptides found in nature. Such high-throughput data collection is best suited to X-ray crystallography using synchrotron radiation. A modern synchrotron source can reduce total data collection to just 30 minutes, as compared with weeks using earlier X-ray–diffraction equipment.

Determining structures by **X-ray diffraction** continues to add to our understanding of DNA replication and protein synthesis. For example, scientists recently studied the crystal structures of a bacterial DNA polymerase I that had DNA primer templates bound to its active site.[13] The enzyme was catalytically active, which allowed for direct observation of the products of several rounds of nucleotide incorporation. The polymerase was able to retain its ability to distinguish between correctly and incorrectly paired nucleotides in the crystal. By comparing the structures of successive complexes, it was possible to determine the structural basis for sequence-independent recognition of correctly formed base pairs.[13]

Ribosomes are the largest asymmetric structures to be solved by X-ray crystallography so far. Results, with resolutions as high as 2.4 Å, have helped establish the locations of the 27 proteins and the 2,833 bases of ribosomal (rRNA) found within the ribosome.[4] The structure also shows that contacts between the two ribosome subunits are limited, which helps explain why the ribosome subunits dissociate so readily.

Some biomolecules or biomolecular complexes are not suitable for diffraction analysis because they cannot be crystallized. Scientists, however, are optimistic about developing techniques to deal effectively with noncrystalline materials.[18] This will make it possible to image everything from cells to individual protein molecules.

4.3 Nuclear magnetic resonance (NMR) spectroscopy

Most people know of magnetic resonance imaging (MRI) as an important diagnostic tool in medicine that can produce incredible images of soft tissues. Less well known is that MRI represents only a limited area of NMR. NMR depends on the fact that atomic nuclei having

an odd number of protons, neutrons, or both have an intrinsic spin. When such a nucleus is placed in a **magnetic field**, it can align either in the same direction as the field or in the opposite direction. A nucleus aligned with the field has a lower energy than one aligned against it. NMR spectroscopy refers to the absorption of **radiofrequency radiation** by nuclei in a strong magnetic field. Absorption of energy causes the nuclei to realign in the higher-energy direction. The nuclei then emit radiation and return to the lower-energy state. The local environment around each nucleus will distort the magnetic field slightly and affect its transition energy. This relationship between transition energy and an atom's position within a molecule allows NMR to provide structural information.

One advantage of NMR spectroscopy over X-ray crystallography and electron microscopy is that it can be applied to the study of movement at the molecular level. NMR studies are providing a growing list of cases where conformational dynamics correlate with protein-protein interaction on surfaces. For example, the enzyme ATP synthase catalyzes the formation of ATP from ADP and phosphate during oxidative phosphorylation in animals and photophosphorylation in plants. This enzyme functions as a molecular motor that uses an internal rotary mechanism. NMR has been used to reveal structural changes in a protein subunit of the enzyme that may explain how the rotation is driven.[20]

Figure 15. Equipment for high-resolution nuclear magnetic resonance (NMR) spectroscopy.

Many see the successful Human Genome Project as providing a foundation for a major initiative in structural biology in which NMR will play a critical role.[5] Informal groups of scientists in the United States are proposing the creation of 10 regional "collaboratories," each with powerful new-generation NMR spectrophotometers to assist with high-throughput structure determinations. Universities, too, are interested in establishing collaborative centers in genomics and proteomics.[9] At Stanford, Nobel Prize–winning physicist Steven Chu and biochemist James Spudich are leading an effort to create an interdisciplinary research center housing 50 faculty members, while Princeton University is planning to add an interdisciplinary genomics institute to its molecular biology department.

4.4 Laser technology

When the laser made its first appearance in the 1950s, it was a tool without a task. Since then, the laser has been put to myriad uses in our everyday lives—from scanning prices at the supermarket to playing music and printing text. Similarly, in scientific research, the laser has found many applications. It is like a Swiss Army knife, having many blades with a variety of uses.

Combining lasers and microscopy has greatly expanded our ability to image cellular and molecular structures. Cells, or parts of cells, can be exposed to antibodies or nucleic acid probes labeled with fluorescent dyes. When excited by laser light of the appropriate wavelength, specific areas of the cell, or regions of a chromosome, can be visualized. The resolution of optical microscopy is limited by physical laws. Diffraction prevents the laser beam (and therefore the spot of fluorescence) from being focused any finer than about 200 nm. However, a new approach is overcoming this limit. It uses a combination of two laser beams, one to illuminate and image the sample, and a second that

shapes the first beam and reduces the effects of diffraction. The technique has been used to distinguish crystals only 100 nm apart and is still undergoing improvement.

Lasers, together with magnets, are being used to develop technologies for manipulating single molecules. Investigators are now able to examine how DNA interacts with the various protein molecules that cut, paste, and copy it. DNA is an ideal choice for single-molecule studies. It is a very large molecule (the longest human chromosome stretches to 9 centimeters) and quite robust. For example, scientists have succeeded in using lasers as optical tweezers to tie knots in single DNA molecules.[2] Results indicate that knotted DNA is stronger than actin, a major muscle protein. Although tying DNA into knots may not seem particularly useful, it does provide insight into the molecule's mechanical properties, which are critical to understanding how enzymes interact with it.

4.5 Simulations and computations

The explosion of data produced by the Human Genome Project led to the creation of a new discipline, bioinformatics, whose focus is on the acquisition, storage, analysis, modeling, and distribution of the many types of information embedded in DNA and protein-sequence data.[14] Biologists are familiar with the terms *in vivo* and *in vitro*, used to describe processes that occur in the body and in the test tube, respectively. Now they are becoming acquainted with a new term, *in silico*, used to describe a new branch of biology that requires little more than a computer and a connection to the Internet. As more and more DNA and protein sequence data find their way into computer databases, the ability of bioinformatics to address biological questions becomes more powerful. The amount of genetic data available and the rate of acquisition are astonishing by any measure. According to Francis Collins, head of the National Human Genome Research Institute, it took four years to obtain the first 1 billion base pairs of human sequence and just four months to get the second billion.[16]

The amount of genetic data available and the rate of acquisition are astonishing by any measure.

The use of computers to model protein folding is one of the primary efforts in the postsequencing phase of the Human Genome Project. In the 1970s, when the first proteins were modeled, the structures generated were *in vacuo* (in a vacuum), with no other molecules interacting with the protein. Of course, each protein in a living cell is surrounded by thousands of water molecules, and these have an important effect on the protein's conformation. Indeed, research has demonstrated that the water-containing models of proteins are much better predictors of how the proteins look and function within a cell.[10]

The importance of protein folding was recently recognized by IBM, which announced that it would spend $100 million to build a supercomputer called Blue Gene. The five-year IBM initiative will involve modeling how proteins take on their three-dimensional shapes. A major aim is to help drug researchers identify drug targets for treating diseases. Protein folding is a daunting problem. Even Blue Gene, which will be 500 times faster than the current fastest computer, will require about one year to simulate the complete folding of a typical protein. The stakes, however, are huge. Approximately one-third of the genes identified in the newly sequenced human genome are of unknown function and are therefore of particular academic and commercial interest. New companies are formed on a monthly basis to take part in this genetics sweepstakes.

5 Technology and the Origins of Molecular Biology

This section provides a brief history of the origins of molecular biology. It addresses the gene's chemical nature, organization, and behavior. Despite molecular biology's narrow focus on DNA, it is readily apparent that many of the most important advances in the field have relied

heavily on technology-based contributions from chemistry and physics. This is addressed in the *National Science Education Standards*. The History and Nature of Science Content Standard G states, "As a result of activities in grades 9 to 12, all students should develop understanding of . . . historical perspectives." It further states, "Occasionally, there are advances in science and technology that have important and long-lasting effects on science and society."

Science historians often attribute the origins of molecular biology to the Phage Group, which first met in 1940 at Cold Spring Harbor Laboratory in Long Island, N.Y. At the center of the group were three scientists. Max Delbrück, a German physicist working at Vanderbilt University, and Salvador Luria, an Italian biologist working at Indiana University, had fled to the United States from Nazi Europe. They were joined at Cold Spring Harbor by Alfred Hershey, an American biologist working for the Carnegie Institution's Department of Genetics.

Bacteriophage, also called phage, are viruses that infect bacteria.[1] These were discovered in 1916 by the English microbiologist F.W. Twort and, independently, two years later by the French-Canadian F. d'Herelle. It was d'Herelle who came up with the name *bacteriophage*. Phage became an important area of research in the 1920s, when scientists hoped they could be used to treat bacterial diseases. When this hope failed to materialize, phage research fell out of favor until the Phage Group resurrected it.[22]

In 1944, Delbrück organized a summer course at Cold Spring Harbor Laboratory to introduce other scientists to the quantitative methods for studying phage that he and Luria had developed. In that same year, the great Austrian physicist Erwin Schrödinger published a book titled *What Is Life?* that discussed heredity from a physics perspective.[19] Schrödinger reasoned that although living things obey the laws of physics, they also might be governed by undiscovered physical laws. Although biologists of that time regarded Schrödinger's book as romantic and a bit naive (for example, he seemed unaware of the important one-gene–one-enzyme work of George Beadle and Edward Tatum from the early 1940s), the book has been credited with influencing a generation of physicists to consider biological questions.

Soon, the ranks of the Phage Group began to grow. It included other physicists, such as Leo Szilard, holder of the patent for the nuclear chain reaction and a participant in the Manhattan Project, and Thomas Anderson, one of the first American electron microscopists. Micrographs obtained by Anderson and Roger Herriott showed that phage begin the infection process by attaching to bacteria by their tails. Later, empty phage "ghosts" could be seen on the bacterial surface.

Hershey and his colleague Martha Chase used phage to examine the molecular nature of the gene.[11] They took advantage of radioactive isotopes that became available as a consequence of work on the atomic bomb. Despite the earlier work of Oswald Avery and his colleagues demonstrating that DNA was the hereditary substance,[3] many scientists continued to believe that genes could only be made of protein. Hershey and Chase began their experiment by using radioactive phosphorous to label phage DNA and radioactive sulfur to label phage protein. They tried to detect which radiolabel went inside the bacterium to direct synthesis of new phage particles after the bacterium was infected. At first, they could not effectively detach the phage particles from the surfaces of the bacterial cells, but then an unexpected technology came to their aid. They used a Waring blender, originally designed to mix cocktails, to disrupt the attachments of the phage to the bacterial cells. The radioactive phosphorous went into the bacterial cells, while the radioactive sulfur remained outside with the phage ghosts, confirming that DNA, and not protein, contains the genetic information. This work set the stage for the contribution of the youngest member of the Phage Group, James Watson.

Watson came to the Cavendish Laboratory at Cambridge University in 1951, ostensibly to

study the three-dimensional structures of proteins. He quickly fell in with Francis Crick, a British physicist, who had developed an interest in heredity after reading Schrödinger's *What Is Life?* The pair formed a collaboration that resulted two years later in the proposal of the double helix model of DNA.[23] Although Watson and Crick relied on model building to solve DNA's structure, they could not have succeeded without help from two other scientists at Cambridge, Maurice Wilkins and Rosalind Franklin. Wilkins first, and then Franklin, used X-ray diffraction to study the structure of DNA. In the case of DNA fibers, the diffraction patterns suggested that the molecule was some type of a helix with a diameter of 20 Å and a repeat of 34 Å. Near the end of the paper that describes the double helix, Watson and Crick included the statement, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

Experimental support for a copying mechanism suggested by the double helix structure came in 1958 from Matthew Meselson and Frank Stahl, then working at the California Institute of Technology. In what some have called "the most elegant experiment in molecular biology," they demonstrated that DNA replicates in a semiconservative fashion, during which one parental DNA strand serves as the template for the synthesis of a new complementary strand.[17] Their ingenious approach involved using a heavy isotope of nitrogen and the ability of density gradient centrifugation to distinguish this heavy form (^{15}N) from the normal light form (^{14}N).

Meselson and Stahl grew *Escherichia coli* in a nutrient medium containing only ^{15}N as a source of nitrogen. DNA replication introduced the heavy isotope of nitrogen into the bacterial DNA. After 14 generations, the bacteria were placed into a medium that contained only ^{14}N as a nitrogen source. During the subsequent replication, the light isotope was incorporated into the bacterial DNA.

Samples of cells were removed before the switch to the light-isotope growth medium (generation 1) and from the first two generations following the switch (generations 2 and 3). DNA samples extracted from the cell samples were centrifuged through a solution of cesium chloride that forms a density gradient during centrifugation (for 20 hours at 40,000 revolutions per minute). DNA molecules form a discrete band at a position where their density equals that of the cesium chloride gradient. The DNA samples taken from generation 1 contained a single heavy band, since both DNA strands contained the ^{15}N isotope. Samples from generation 2 displayed a single band of medium density, since each DNA molecule consisted of one heavy (^{15}N) parental strand and one light (^{14}N) complementary strand. Finally, samples from generation 3 displayed bands of two different densities. One band of medium density again consisted of a heavy parental strand and a new complementary light strand. A second band of light density consisted of two strands of light DNA, one an inherited light parental strand and the other, a new complementary light strand.

Around the time that Meselson and Stahl were performing their experiments, Crick theorized that genetic information flow resided in DNA, passed through an RNA intermediate, and became expressed as a sequence of amino acids. Using the electron microscope, it was possible to visualize DNA and RNA molecules that first had been stained with heavy metals. Using extracts from bacteria, scientists were able to glimpse Crick's "central dogma" in action. Micrographs were obtained that showed newly synthesized RNA molecules branching off from a transcribed region of DNA. Furthermore, ribosomes could be seen already attaching to the growing RNA chains. Not only did electron microscopy provide this comprehensive view of gene expression, it also was about to produce critical insight into gene organization.

In 1977, the laboratories of Phillip Sharp and Richard Roberts independently used the electron microscope to make a fundamental

discovery about gene organization and expression. First in adenovirus, and later in eukaryotic DNA, it was shown that some genes are interrupted by stretches of DNA that are not represented in the messenger RNA (mRNA). For example, DNA containing the gene for ovalbumin was denatured and hybridized to ovalbumin mRNA. Electron micrographs of the hybrid revealed regions of heteroduplex formation alternating with a series of seven loops that corresponded to regions of genomic DNA that have complementary sequences in the mRNA. The regions of a gene found in the mRNA are called exons, because they are expressed in the gene product. Regions not found in the mRNA are called introns, because they are located in between the exons.

The origins and early development of molecular biology would not have been possible without biophysical techniques such as X-ray diffraction, electron microscopy, and isotope labeling. These techniques, along with others, continue to be refined and extended to new areas of biology. As biology becomes more data intensive, it relies increasingly on biophysical techniques.

The completion of the Human Genome Project marks the end of the effort to decode the entire set of human genes. It also marks the unofficial start of the next phase of our continuing quest to understand how genetics contributes to human health and well-being. Biology underwent a paradigm shift more than 30 years ago after the discovery of restriction enzymes. These enzymes are just tools, yet they helped shift biology from a largely descriptive science to a manipulative one. In a similar way, the rise of structural biology is helping propel biology toward another paradigm shift. Currently, over 500,000 human DNA sequences are contained in genetic databases. It is estimated that these may give rise to 160,000 targets for drug development.

6 The Goal of This Supplement

The goal of this curriculum supplement is to help prepare high school biology students for the technological world they will inherit. This is consistent with the *National Science Education Standards*. For example, Science and Technology Content Standard E states, "As a result of activities in grades 9 to 12, all students should develop . . . understandings about science and technology." A fundamental concept that underlies this standard is that science advances with the introduction of new technologies, and solving technological problems results in new scientific knowledge. New technologies also extend scientific understandings and introduce new areas of research.

The technologies presented in this supplement are new to most high school students. Very few students will have had much exposure to chemistry or physics, and students in your classes will be spending only about a week with this supplement. A detailed understanding of each technique should *not* be the primary objective of the supplement. Rather, students should come away from it with an appreciation of some of the applications and implications of technology in the study of cellular and molecular biology.

Glossary

angstrom: Unit of measurement defined as 1×10^{-10} meter and represented by the symbol Å; a sheet of paper is about 1,000,000 Å thick.

bacteriophage: Viruses that infect bacteria.

bioinformatics: The study of the inherent structure of biological information and biological systems. It brings together biological data from genome research with the theory and tools of mathematics and computer science.

infectious agent: A living organism that enters and multiplies in a host (that is, produces an infection); the infection can be without symptoms, or it can produce disease.

laser: A device that produces a narrow, powerful beam of light.

magnetic field: A region in space created by moving electrons (that is, an electric current); this produces a force that causes other electrons to move, thus creating another electric current.

micrograph: A graphic reproduction of the image of an object formed by a microscope.

nanometer: Unit of measurement defined as 1×10^{-9} meter and represented by the abbreviation nm.

pathogen: An agent, such as bacteria, viruses, and fungi, that produces disease.

pathology: The study of disease or any condition that affects the length or quality of life.

probe: An exploratory device, especially one designed to investigate and obtain information about an unknown region or object.

radiofrequency radiation: Electromagnetic waves with a wavelength of 1 millimeter to 30 meters.

rational drug design: See target-based drug design.

resolution: A measure of the ability of a system to form separate and distinct images of two objects of a given angular separation.

scale: A series of ascending and descending steps to assess the relative or absolute size of some property of an object. Scales can be linear or logarithmic.

spectroscopy: The study of the distribution of a characteristic of a system or phenomenon, especially the distribution of energy emitted by a system or the distribution of atomic or subatomic particles in a system.

striated muscle: Muscle tissue, such as skeletal muscle, that is made up of long fibers and is characterized by alternating light and dark bands.

synchrotron: A name given to X-rays or light produced by electrons circulating at nearly the speed of light. These can be used to investigate atomic and molecular structure.

target-based drug design: Also called rational drug design, an approach based on the

development of molecules (potential drugs) to interact specifically with a biological structure involved in disease. The biological structure may be a pathogen, a product of the pathogen (such as a protein), or a molecule (such as a protein or other disease-causing molecule) of a host cell that interacts with a pathogen or a pathogen product.

technology: A body of knowledge used to create tools, develop skills, and extract or collect materials; the application of science (the combination of the scientific method and material) to meet an objective or solve a problem.

wavelength: The distance between one peak of a wave of light, heat, or other energy and the next corresponding peak.

X-ray: Electromagnetic energy having a wavelength in the approximate range from 0.01 to 10 nanometers.

X-ray diffraction: The scattering of X-rays by crystal atoms that produces a pattern that yields information about the structure of the crystal. The wavelengths of X-rays are comparable in size to the distances between atoms in most crystals. X-ray diffraction is the basis of X-ray crystallography.

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What Is Technology?

Lesson 1
Engage
Explore
Explain

At a Glance

Overview

This lesson consists of two activities linked by classroom discussion. Its purpose is to engage students in the general topic of technology. The first activity involves classroom discussion and a short scenario to allow students to develop a sense of what technology is and to dispel the notion that technology relates mostly to computers. The second activity introduces students to the concept of scale by using the classroom to represent a cell and other smaller objects to represent subcellular components.

Major Concepts

Technology is a body of knowledge used to create tools, develop skills, and extract or collect materials. It is also the application of science (the combination of the scientific method and material) to meet an objective or solve a problem. Scale is a way to represent the relationship between the actual size of an object and how that size is characterized, either numerically or visually.

Objectives

After completing this lesson, students will

- be able to explain what technology is,
- recognize that human intervention is the common bond among technologies, and
- describe the use of **scale** to distinguish between objects of different size.

Teacher Background

See the following sections in Information about Using Technology to Study Cellular and Molecular Biology:

1 Introduction *(page 23)*

2 Major Preconceptions *(pages 23–24)*

3.1 Scale *(pages 24–25)*

In Advance

Web-Based Activities

Activity	Web Version
1	No
2	No

Photocopies

Activity 1	none
Activity 2	Master 1.1, *Searching for Scale*, 1 copy per student

Materials

Activity 1	none needed
Activity 2	• meter stick • rulers • objects of various sizes (see Teacher note on page 49)

Preparation

Activity 1
No preparations needed.

Activity 2
No preparations needed.

Procedure

Assessment:
This activity is designed to engage students in learning about technology and to help the teacher assess the students' prior knowledge of the subject.

Activity 1: *Technology—What's It All About?*

Tip from the field test: Activities 1 and 2 can be conducted in several ways. You can engage the class as a whole in discussion as directed. Alternatively, you can divide the class into groups of three to five students each, ask each group to consider the questions you ask, and then have each group provide its responses. It is also possible to have student groups consider only a limited number of the questions and then handle the remainder with the whole class. If you choose either of the last two approaches, you should limit the time allotted for groups to consider each question to several minutes. Field-testing indicated that no approach was superior to another.

1. **Begin by asking the class, "How do you define *technology*?"**

   Accept all answers and write student responses on the board. Do not attempt to have students refine their definitions of technology at this point. They will revisit their definitions and refine them in

Step 5. Students, like older individuals, may harbor the preconception that technology relates mostly to computers. Through advertisements and media articles, they are familiar with the terms *information technology* and *computer technology*.

Teacher note: Asking this question requires students to call on their prior knowledge, and it engages their thinking. At this point, do not critique student responses. Appropriate teacher comments are short and positive, such as "good" and "what else?" Other appropriate teacher responses include, "Why do you believe that?" or "How do you know that?" Questions such as these allow the teacher to assess students' current knowledge about the subject and to adjust lessons accordingly. They also provide a springboard to "Let's find out" or "Let's investigate." In general, it is time to move forward when the teacher sees that thinking has been engaged.

2. **Ask students, "In general, what does technology do for us?"**

   This question may help students understand that technology helps us solve problems, makes our lives easier, and extends our abilities to do things. Technology is used to develop skills or tools, both in our daily lives and in our occupations.

3. **Focus discussion on technologies that are relevant to each student's life. Ask students to look around the room. What technologies do they see? How do these technologies solve problems and make their lives easier?**

   Accept all responses and write them on the board. Students may mention any number of items. Some may be school-related, such as binders, backpacks, pens, pencils, paper, and paper clips. Other items may be more personal, such as water bottles, personal stereos, and hair clips. Students may neglect items such as shoelaces, zippers, buttons, fabric, eyeglasses or contact lenses, makeup, and bandages. Discussion should reinforce the notion that humans develop technology with a specific objective in mind. A related concept is that a given task requires the right tool or tools.

4. **Pick a technology that students have mentioned. Ask them what types of knowledge were required to develop that technology.**

   Students may not realize that technologies are generally developed by applying knowledge from multiple disciplines. For example, producing today's audio devices, such as a portable CD player, requires knowledge obtained from engineering, physics, mathematics, chemistry, and computer science.

5. **On the basis of previous discussions, ask students to rethink and refine their definition of technology (from Step 1).**

Students should mention that technology is a way of solving problems through the application of knowledge from multiple disciplines.

6. **Tell students to imagine that they live in the Stone Age. Their only garment has been ripped and requires mending. How would they do it?**

   Students first should recognize that the ripped garment is a problem requiring a solution. They should consider what technologies they have available. The Stone Age was a period early in the development of human cultures when tools were made of stone and bone. Clothing consisted of animal skins or fabrics woven from threads derived from plant fibers. Bones and sharp reeds were used to make needles.

Content Standard E: Technological design is driven by the need to meet human needs and solve human problems.

7. **Ask students how their approach to mending the garment would change as time advanced from the Stone Age to the present. What new knowledge would allow the development of new technology?**

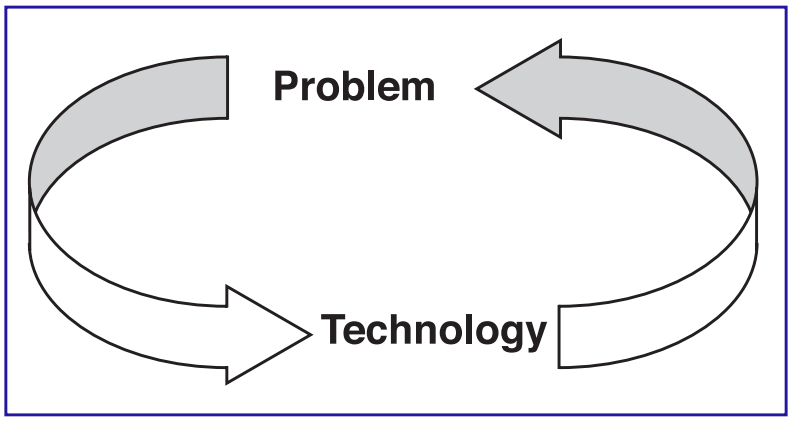
   Student responses will vary, and some students may want to jump directly from the Stone Age to the modern sewing machine. Slow them down and have them consider incremental changes in knowledge and technologies. They may cite the use of metals to fashion repair tools, like knives and finer needles. New knowledge of metals and chemistry would help here. Later advances in engineering and mechanics would lead to the development of human-run machines for assisting with repairs. Eventually, advances in physics (electricity) and engineering led to the invention of modern sewing machines. Similarly, advances in agriculture, chemistry, and engineering produced better fabrics and threads. Students should derive an understanding that technology advances through interactions among multiple disciplines. While a problem may remain basically the same over time (for instance, the need to make or repair clothing), advances in technology change how the problem is solved.

Assessment: Listening to students' responses will help you assess their understanding of the relationship between problems and technology.

8. **Write the words *problem* and *technology* on the board. Ask students to use arrows to draw a graphic that represents the relationship they believe exists between a problem and the technology to solve it.**

   They can use arrows of any kind, and they should be prepared to defend their suggestions. The graphic should illustrate that a

problem does not drive technology unidirectionally, nor does technology exist solely in search of a problem to solve. Rather, these two areas exist to support and drive one another. Solving problems does require the development of new technologies, which can then be applied to other problems. A graphic to depict this indicates the cyclic relationship between the two:



Activity 2: *Searching for Scale*

1. **Biological molecules are small, but how small *is* "small"? Ask students these two questions:**

   a. **How do biological structures, such as cells, organelles, bacteria, and viruses, compare in size with one another?**

   b. **How do molecules compare in size with biological structures such as cells, organelles, bacteria, and viruses?**

   Accept all responses and write them on the board. Students will explore these size relationships in the next steps.

2. **Tell students that they will now investigate the relative sizes of different biological structures and see how close their estimates of relative size were.**

3. **Give each student a copy of Master 1.1, *Searching for Scale*. Work with the class to complete column 3, Size relative to cell.**

   The table with column 3 completed is as follows:

Biological Structure	Actual Diameter (in Meters)	Size Relative to Cell	Object Used to Model Biological Structure	Measured Size of Model Object	Size Relative to Model Cell (the Room)
Cell	1×10^{-5}	$\frac{1 \times 10^{-5}}{1 \times 10^{-5}} = 1$	Room	10 m	$\frac{10}{10} = 1$
Bacterium	1×10^{-6}	$\frac{1 \times 10^{-6}}{1 \times 10^{-5}} = \frac{1}{10}$	Desk	1 m	$\frac{1}{10} = \frac{1}{10}$
Mitochondrion	5×10^{-7}	$\frac{5 \times 10^{-7}}{1 \times 10^{-5}} = \frac{1}{20}$		0.5 m	
Virus	1×10^{-7}	$\frac{1 \times 10^{-7}}{1 \times 10^{-5}} = \frac{1}{100}$		0.1 m (10 cm)	
Ribosome	1×10^{-8}	$\frac{1 \times 10^{-8}}{1 \times 10^{-5}} = \frac{1}{1{,}000}$		0.01 m (1 cm)	
Protein	5×10^{-9}	$\frac{5 \times 10^{-9}}{1 \times 10^{-5}} = \frac{1}{2{,}000}$		0.5 cm	
Glucose molecule	1×10^{-9}	$\frac{1 \times 10^{-9}}{1 \times 10^{-5}} = \frac{1}{10{,}000}$		0.1 cm (1 mm)	
H_2O molecule	1×10^{-10}	$\frac{1 \times 10^{-10}}{1 \times 10^{-5}} = \frac{1}{100{,}000}$		0.1 mm	

Content Standard A: Mathematics is essential in all aspects of scientific inquiry.

4. **Tell students that the information in columns 2 and 3 each can be used to construct *scales* to describe the sizes of the different biological structures in the table. Ask students to define *scale*.**

   Accept all answers and write them on the board. Guide discussion so that students realize that scale is a way to represent the relationship between the actual size of an object (for example, its length or mass) and how that size is characterized either numerically or visually. A scale is a series of ascending and descending steps to assess either some relative (column 3) or absolute (column 2) property of an object. In this case, the property being investigated is size.

5. **Ask students to try to visualize the 100,000-fold difference in size between a cell and a water molecule. Can they do it? How could they demonstrate this large size difference more easily?**

   Master 1.1, *Searching for Scale* provides the necessary clues for students, since the heading of column 4 is *Object used to model biological structure*. Students can use larger structures, such as a room, to model smaller ones, such as a cell, to make size differences more apparent and bring them into the realm of common experience.

6. **Ask two students to use a meter stick to mark approximately 10 m along both the length and width of the classroom.**

It is okay if the classroom does not allow 10 m to be measured in either or both directions. A distance of 7 to 9 m will still make the point visually. However, for ease of calculations to follow, use room dimensions of 10 m even if the actual dimensions are smaller than that.

7. **Tell students that the space defined by 10 m wide, 10 m in length, and the height of the room now represents a cell. In other words, this space is now a *model* for a typical cell.**

8. **Organize students into pairs and give each pair a ruler.**

9. **Tell students that they will be searching the classroom for objects that model the biological structures on Master 1.1, *Searching for Scale*.**

   Explain that they will be looking for objects that have the same size relative to the model cell (the room) that the actual biological structure has to a real cell.

10. **Ask students to look at the last three columns on Master 1.1, *Searching for Scale*. As an example, a desk measuring 1 meter high is provided as a model for a bacterium. Important points are as follows:**

    a. **A bacterium is $\frac{1}{10}$ the size of an actual cell (column 3).**

    b. **Similarly, the desk is $\frac{1}{10}$ the size of the model cell, the room (1 m compared with 10 m; columns 4 and 5).**

    c. **Because it is of the correct scale, the desk can be used to model a bacterium if a cell is modeled by a room 10 m across.**

11. **Instruct student pairs to locate items in the classroom that can be used to model the biological structures listed on Master 1.1, *Searching for Scale*. They should enter their results in columns 4, 5, and 6 of the master. Allow 15 minutes for this activity.**

    Students may approach this activity in different ways. Some may find it useful to determine the size of the object they are looking for first by multiplying the ratio in column 3 by 10 m. Some students may begin by locating objects, measuring them, and then determining whether they meet the size requirements.

    Teacher note: It is helpful to have objects available in the classroom that will meet the size requirements for modeling the biological structures in Master 1.1. Objects, such as erasers, marbles,

Content Standard A: Recognize and analyze alternative explanations and models.

Assessment: Circulate around the room, noting whether students understand the mathematics involved in scaling objects for this activity.

Assessment: Listening to student responses will help you assess their understanding of scale and modeling. Collecting their completed tables (Master 1.1, *Searching for Scale*) allows a more formal opportunity to evaluate students' understanding.

fine- and ultrafine-tip pencils or pens, pieces of candy, an inflated balloon, balls of different sizes, and other easily obtained materials, ensure that students will be able to find something to serve as a model for each structure.

12. **Ask student pairs to share some of their results with the class.**

    Students should realize that the size ratios in columns 3 and 6 are the same. In other words, modeling allows *relative* sizes to be studied, although the *actual* sizes of the real biological structure and its model differ quite a bit.

Discussion Questions

1. **If a cell of 1×10^{-5} m (10×10^{-6} m, or 10 µm) diameter is represented by a room 10 m across, what distance would represent a human 2 m tall?**

   First, as in column 3 of Master 1.1, *Searching for Scale*, derive the relationship between the size of the human and the size of the cell:

   $$2 \text{ meters} \div (1 \times 10^{-5} \text{ meter}) = 2 \times 10^{5}.$$

   Thus, a 2-m-tall individual is 2×10^{5} times larger than a cell 1×10^{-5} m in diameter.

   If the cell is represented by a distance of 10 m, the 2-m-tall individual would be represented by a distance of

   $$10 \text{ m} \times (2 \times 10^{5}) = 2 \times 10^{6} \text{ m (2,000 km, or 1,250 miles)}$$

   As a reference, this distance is the same as that from Boston to Miami, Kansas City to Boston, or Los Angeles to Dallas. This calculation is intended to provide a "wow" for the students, and they derive an understanding of the difference in size between a human and a molecule (in this example, the difference between 2,000,000 m for the human and 2 to 5 mm for a protein). This should help students understand the need for specialized technologies for studying living systems at the cellular and molecular levels.

2. **As a lead-in to Lesson 2, write the following terms on the board in random order: Eye; Light Microscopy; Electron Microscopy; X-ray Techniques. Ask students to speculate on which technology (or technologies) could provide useful information about the objects on Master 1.1, *Searching for Scale*. What would make one technology more useful than another in any given situation?**

   Students should realize that naked-eye observation is useful only for relatively large objects and is not useful at all for discerning cellular and subcellular objects. They also will realize that light microscopy is useful for looking at cells and resolving some

organelles, like the nucleus and vacuoles. Students should know from material in their texts that electron microscopy is used to provide details about cells and subcellular structures. Some may have seen electron micrographs of DNA. Most students know little about X-ray technologies, although they may have heard of X-ray crystallography as a technique that was used to help resolve the structure of DNA. If students have ideas about why certain technologies are better for some tasks than others, write those responses on the board. Indicate that the reason for having the right tool for the right task is addressed in Lesson 2.

Lesson 1 Organizer

Activity 1: *Technology—What's It All About?*

What the Teacher Does	Procedure Reference
Ask students, • "What is technology?" • "In general, what does technology do for us?"	Pages 44–45 Steps 1–2
Focus discussion of technologies relevant to each student's life. • Ask students to look around the room; what technologies do they see? • How do these technologies solve problems and make their lives easier? • Pick a technology mentioned. Ask students what types of knowledge were required to develop that technology. • After discussion, ask students to rethink and refine their definition of technology.	Pages 45–46 Steps 3–5
Tell students to imagine that they live in the Stone Age. Their only garment is ripped and requires mending. Ask, • "How would you mend the garment?" • "How would your approach to mending the garment change as time advanced from the Stone Age to the present?" • "What new knowledge would allow the development of new technology?"	Page 46 Steps 6–7
Write the words *problem* and *technology* on the board. Ask students to use arrows to draw a graphic that represents the relationship they believe exists between a problem and the technology needed to solve it.	Page 46 Step 8

Activity 2: *Searching for Scale*

What the Teacher Does	Procedure Reference
Ask students, • "How do biological structures, such as cells, organelles, bacteria, and viruses, compare in size with one another?" • "How do molecules compare in size with biological structures such as cells, organelles, bacteria, and viruses?"	Page 47 Step 1

Tell students that they will investigate the relative sizes of different biological structures. • Give each student a copy of Master 1.1, *Searching for Scale.* • Work with the class to complete column 3, Size relative to cell. • Ask students to define *scale* based on the information in columns 2 and 3. • Ask students if they can visualize the 100,000-fold difference in size between a cell and a water molecule. How could they demonstrate this large size difference?	Pages 47–48 Steps 2–5 M
• Ask two students to measure and mark approximately 10 m along both the length and width of the classroom. • Tell students that the space defined by 10 m wide, 10 m in length, and the height of the room is a model for a typical cell.	Pages 48–49 Steps 6–7
Organize students into pairs. • Give each pair a ruler. • Tell students that they will be searching the classroom for objects that model the biological structures on Master 1.1, *Searching for Scale.* • Tell students to use the information provided in the last three columns of Master 1.1 to help in their search. • Instruct students to complete the last three columns of Master 1.1 as they locate appropriate objects.	Pages 49–50 Steps 8–11
Ask students to share some of their results with the class.	Page 50 Step 12

M = Involves copying a master.

Lesson 2
Explore
Explain

Resolving Issues

At a Glance

Overview

This lesson consists of two activities linked by classroom discussion. In the first activity, which is similar to the game Battleship, students investigate the concept of resolution and the relationship between probe size and resolution. The second activity incorporates results from the first activity and classroom observation and discussion. Students discover that in order to understand the complete structure of an object, it is necessary to have information in three dimensions rather than just two.

Major Concepts

Doing research in cellular and molecular biology requires scientists to identify the right technology (tool) for the job. An important consideration is the technology's ability to resolve structural details of biological objects. Two objects can be resolved by using a probe (radiation) of a size (wavelength) that is not larger than the distance separating the objects. Generally, the smaller the probe, the greater the structural detail, or resolution, that results. Detailed structural knowledge about biological objects requires information obtained in three dimensions.

Objectives

After completing this lesson, students will

- be able to define resolution,
- be able to explain the relationship between probe size and resolution, and
- be able to explain why information in three dimensions is necessary to describe the structure of an object.

Teacher Background

See the following sections in Information about Using Technology to Study Cellular and Molecular Biology:

3.1 Scale *(pages 24–25)*

3.2 Resolution *(pages 25–26)*

In Advance

Web-Based Activities

Activity	Web Version
1	No
2	Yes

Photocopies

Activity 1	• Master 2.1, *Probing for Answers Score Sheet*, 1 copy per 2 students; 1 transparency for classroom demonstration • Master 2.2, *Probes*, 1 copy per 12 students (see Preparation) • Masters 2.3 to 2.8, *Probing for Answers—Levels 1–6*, 1 copy of each per 12 or fewer students; 2 copies of each for 13–24 students; 3 copies of each for 25–36 students
Activity 2	• Master 2.9, *Solution to Probing for Answers*, 1 transparency (*print version* only)

Materials

Activity 1	manila folders (1 per group, optional)
Activity 2	• 2 hard-crusted bread rolls, unsliced • knife to slice bread • food coloring • syringe with needle, or 1-mL pipette

Preparation

Activity 1

From Master 2.2, *Probes*, cut out each 3 × 3, 2 × 2, and 1 × 1 square (1 copy produces 6 of each size of probe).

Activity 2

Just before the class period in which students will do this activity, inject a small amount of colored food dye into two locations in each of two unsliced, hard-crusted bread rolls. One location should be to the right of center and the other, to the left of center. The same or different dye colors can by used. Injecting the dye can be accomplished several ways to meet the primary objective, which is to color the inside and not the outside of each roll. Use either a syringe with a needle long enough to reach well into the roll or a carefully inserted 1-mL pipette. Wipe the outside surface of the needle or pipette to remove any dye solution before inserting it into the roll. It may help to use a sharp object, such as the sharp, pointed portion of a compass, to make a small hole before inserting a pipette containing dye. Try not to leave traces of the dye on the outside of the rolls.

If you have Internet access, have at least one computer at the URL *http://science.education.nih.gov/supplements/technology/student*. This is a main menu page from which you can access this activity.

Activity 1: *Probing for Answers*

Procedure

1. **Begin by stating or writing on the board, "Technology is a means of extending human potential or of extending human senses." Ask students to raise their hands if they agree with this statement.**

2. **Ask students to provide justification for their responses. Can students relate specific technologies to the extension of specific human attributes or senses?**

   Students will generally agree that technology extends human potential. Obvious examples include the wheel and other transportation innovations that extend our potential for movement, and electronic devices, such as TV, radio, and telephones, that extend our ability to communicate. Microscopes, telescopes, eyeglasses, and contact lenses extend and enhance our sense of vision. Computers and written materials can be seen as ways to extend memory. There are many other examples.

   Tip from the field test: Some students correctly pointed out that technology is also used to extend animal potential.

3. **Ask students to consider only technologies that have increased our understanding of living systems. Do they extend any human attributes? If they do, which attributes are extended?**

   Students will probably focus on those that extend vision, since they are the easiest to recognize. Examples could include radar, eyeglasses, contact lenses, and telescopes. Students also know that microscopes allow us to see objects that we cannot see with the naked eye. Students should be familiar with the light microscope, and many may have heard of electron microscopes. Through figures in textbooks, they may know X-ray crystallography as a technology that helped us "see" the structure of DNA. Other technologies might be mentioned. Accept all responses and write them on the board. This is an opportunity to identify students' current understanding of these technologies.

   A Gary Larson Far Side cartoon, "Early Microbiologists," can be used to engage students. Pictured is a caveman "laboratory," in which several cavemen peer intently into Petri dishes filled with agar. Since they do not have microscopes, they hold the dishes in various ways, such as very close to the face. One of the cavemen

Assessment:
Steps 1 to 5 are intended to be a quick method to assess students' prior conceptions about the use of technology in biological science.

imitates binoculars by holding his hands to his eyes. (The cartoon can be found in several published works, including *The Prehistory of the Far Side*, by Gary Larson, copyright 1989 by FarWorks, Inc., distributed by Universal Press Syndicate, published by Andrews McMeel, Kansas City, Kansas.)

4. **Ask students to focus on technologies as tools that allow us to "see" biological objects (the eye, microscopes of all kinds, and X-ray techniques). *One at a time*, ask the following questions:**

   a. **What technologies would you use to study a whole (intact) organism and why?**

   b. **What technologies would you use to study cells and why?**

   c. **What technologies would you use to study molecules and why?**

   Accept all reasonable responses, but challenge those that are incorrect. Students should understand that no single technology is useful at all levels of organization of biological organisms. In other words, no single technology is able to resolve structural details from the intact organism to the molecules that make up that organism. This discussion introduces students to the idea that there is a right tool for the job.

Content Standard A: Identify questions and concepts that guide scientific investigations.

5. **Ask students why a single technology cannot provide information at all levels of organization of biological organisms.**

   You might remind students that at the conclusion of Lesson 1, they were asked to speculate on what would make one technology more useful than another in a given situation. If students need prodding, you can ask whether they would use a microscope to study a whole organism, or whether they would use their eyes alone to study molecules. While a microscope is required to study single-celled organisms, such as bacteria and protists, most multicellular organisms can be observed with the unaided eye. High-resolution technologies, such as X-ray crystallography, are required for investigations of molecular structure.

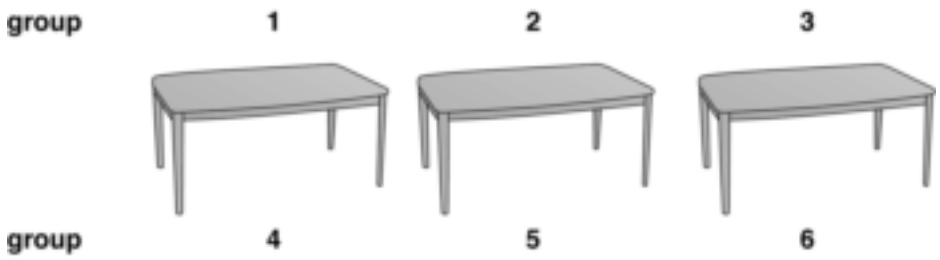
6. **Tell students that what makes some technologies better than others for a given job relates to the concept of "resolution." Ask them what *resolution* means.**

   Tip from the field test: Students generally had no concept of resolution as it relates to technologies used in biological science. Responses often related to resolution of computer monitors, personal resolve, or New Year's resolutions.

7. **Tell students that they will investigate resolution. Organize the class into groups of two and then pair two groups.**

   This activity works best if you have a minimum of six groups so that each can receive one of the six Masters 2.3 through 2.8.

8. **Ask groups to arrange their seating so that one is directly opposite another:**



   Allow sufficient room between tables so that groups do not interfere with one another.

9. **Explain to the class that this activity resembles the game Battleship, with which some of them might be familiar. Each group's task is to locate and define the shape of an object or objects on the master held by the opposing group.**

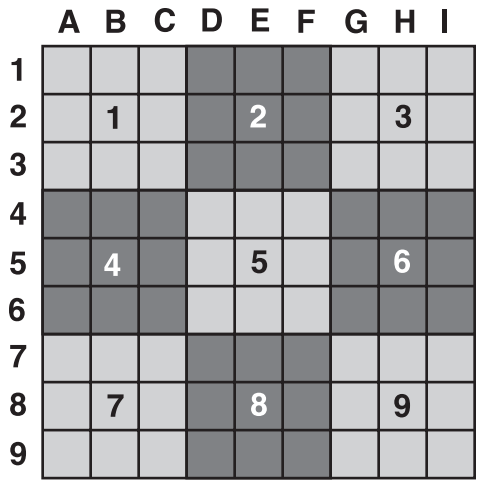
   Tip from the field test: Field-testing indicated the need to point out that this activity is not exactly like Battleship. Students do not "sink" or "destroy" an opposition's force. Rather, they use the Battleship strategy to locate and define the shape of a shaded region or regions on the master held by an opposing group.

10. **Give each group a copy of Master 2.1, *Probing for Answers Score Sheet*.**

    Students use this sheet to record hits and misses as they probe for the location of the opposing group's shaded region(s).

11. **Randomly color several regions on a transparency of Master 2.1, *Probing for Answers Score Sheet*. Use this transparency and a 3 × 3 probe from Master 2.2, *Probes*, to demonstrate how this activity is done.**

    a. **Use this probe to locate areas 3 squares by 3 squares on the transparency. To save time, you may instruct students to probe only the nine nonoverlapping 3 × 3 regions, as shown on the following diagram:**



b. One group begins by calling out the location of the 3 × 3 area they wish to probe, such as A-C, 1-3.

c. If the opposing group's Master (2.3, 2.4, 2.5, 2.6, 2.7, or 2.8) has a shaded square within the area called, they indicate this as a hit; if not, a miss.

d. The first group records the result on their score sheet. Draw an X in 3 × 3 squares that are misses, and put an O in the 3 × 3 squares that are hits.

e. It is then the opposing group's turn to select an area to probe, which is then recorded as a hit or a miss.

f. Groups take turns trying to locate the opposing group's shaded squares.

12. **Give each group a copy of *one* master selected from Masters 2.3 to 2.8. Instruct groups to hide this master from their opposing group.**

    Make sure that each of these six masters is used by at least one group. In larger classes, the same master may be used by more than one group. You may choose to place each master in a manila folder. Students can use the folder in various ways (for instance, opened and stood on its edge) to keep their master from being seen by the opposing group.

13. **Give each group a 3 × 3 probe from Master 2.2, *Probes*. Instruct students to use this probe to locate areas 3 squares by 3 squares that contain the opposing group's shaded area(s).**

    Limit the time allowed for this portion of the activity to no more than five minutes.

14. **Ask students whether they believe they have gathered enough information to specify the *exact* shape(s) and location(s) of the opposing group's shaded object(s).**

    Make sure students in opposing groups do not share information about their shaded patterns. Students should realize from looking at their own shaded pattern that the 3 × 3 probe is too large to identify the shape and location of smaller objects; that is, the large probe cannot resolve the size and shape of the smaller objects.

15. **Ask students what would help them define the shape and location of the opposing group's shaded object(s).**

    A smaller probe is required.

    Tip from the field test: Field-testing indicated the importance of having students come to this conclusion on their own.

16. **Next, give each group a 2 × 2 probe. Groups are to focus on those areas that were determined to be hits with the larger probe.**

    Students are to repeat with this probe what they did earlier (see Step 13 above) and try to determine the structure and location of the opposing group's shaded pattern. Limit the time allowed for this portion of the activity to no more than several minutes.

17. **Ask students whether they believe they now have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s).**

    Make sure students in opposing groups do not share information about their shaded patterns. At this point, some students may believe they have sufficient information to predict the pattern held by the opposing group. Ask those willing to speculate on the opposing group's pattern to provide their justification, especially how they know that all four squares in a 2 × 2 "hit" region are shaded.

18. **Next give each group a 1 × 1 probe.**

    Students should focus only on those areas determined to be hits with the 2 × 2 probe. They should continue to define the structure and location of the opposing group's shaded pattern. Limit the time allowed for this portion of the activity to no more than several minutes.

19. **Ask students if they believe they now have gathered enough information to specify the exact shape(s) and location(s) of the opposing group's shaded objects. Do they need another probe to complete the task?**

Students should justify their responses. Students cannot know for sure what the opposing group's pattern looks like, even though they see that their own pattern is composed of 1 × 1 squares. If they speculate that the opposing group's pattern is constructed similarly, then no additional probes are required, since the objects being resolved (the 1 × 1 squares, both shaded and unshaded) are the same size as the final probe. Importantly, the final probe is not larger than the objects being resolved. If students believe that additional probes are required, they should justify this based on what they believe to be the size of the objects being resolved (shaded and unshaded). Their suggestion for an additional probe should indicate a probe size no larger than that of the objects being resolved. No matter what the response, ensure that students derive a general relationship between probe size and the size of the objects being resolved before proceeding. They should be able to explain that the size of the probe should be no larger than the objects being resolved.

Assessment: Listening to students explain their answers, defend their reasoning, and modify their responses after listening to other students explain their logic will help you assess students' understanding of resolution.

20. **Have opposing groups confirm that after using the series of three probes, they were able to determine the correct pattern on one another's master.**

Discussion Questions

1. **Why not use the smallest probe first?**

   A similar question is, Is there an advantage to using larger probes first and then using smaller probes? The larger probes allowed the students to quickly identify the general location of the object(s) being investigated. In some cases, even information about structure, albeit crude, can be obtained. Remind students of the procedure they follow when using a light microscope. They first use the lowest magnification to locate the object of interest and then switch to a higher magnification to gain more information. Using the smallest possible probe first can be time consuming and expensive. In some cases, using the smallest available probe also can be inappropriate; for example, when the probe is very much smaller than the objects being resolved. As an example, consider the time and expense involved in using an electron microscope rather than a light microscope to count yeast cells or to assess fruit fly traits in a genetics experiment.

2. **On the board, write these wavelengths:**
   - **visible light, 4 to 7 × 10^{-7} m;**
   - **electrons, 2.7 to 0.9 × 10^{-10} m; and**
   - **X-rays, 1 × 10^{-8} to 1 × 10^{-11} m.**

   Refer to Master 1.1, *Searching for Scale,* and ask students which

of these they think would be appropriate probes (that is, provide the appropriate level of resolution) for the objects listed.

Visible light could be used to resolve cells, bacteria, and mitochondria. Longer-wavelength electrons are potential probes for viruses, small cell organelles such as ribosomes, and large molecules such as proteins. Shorter-wavelength electrons and short-wavelength X-rays are potential probes for molecules, even small ones like glucose. They also may be used to resolve adjacent atoms in molecules (which requires probes smaller than 2×10^{-10} m).

Teacher note: Whether or not a probe is useful in a given situation also depends on whether the technology actually exists to make use of the probe. For instance, are appropriate sample-preparation techniques available? Are appropriate sample handling technologies available (for example, can the sample be rotated if necessary, and in a way that does not interfere with the rest of the procedure)? Can the probe be focused sufficiently? Is there technology to view and evaluate the results of such analyses?

Activity 2: *More Than Meets the Eye*

1. **Begin by holding one of the bread rolls up to the class. Make sure that no dye is showing. Ask students to describe what they see.**

   Students will recognize the object, and they may describe it by noting its color, shape, and apparent external texture. They should indicate that the roll is a three-dimensional object.

2. **Do students have maximum information about the roll? Is there anything they do not know about the bread roll from just looking at it?**

   Student responses will vary from, "Is it tasty?" and "Where does it come from?" to "What is inside?" Some students may realize that although they might have made an assumption about the roll's interior (for example, it is just plain bread), they actually know nothing about what is under the crust.

3. **Focus discussion on what is inside the bread roll. Ask students how they would get that information.**

   Students will suggest cutting or tearing the roll.

4. **Slice the roll to reveal the presence of dye in one of the two dye locations. Hold the roll so the class can see**

the two cut edges. Do the students now feel they have complete information about this object? If not, what questions do they have?

Even though they know there is a dyed region inside the roll, students should realize that they do not know what this region looks like. What is the shape of the dyed region and how far does it extend in any given direction? Is there only a single dyed region, or are there multiple regions? If there is more than one dyed region, is it the same color as the region they can see?

Tip from the field test: Some students suggested cutting the roll as one would if making a sandwich. The second bread roll is helpful if this possibility is raised.

5. **Ask students how they could obtain information to answer these questions.**

   A simple approach would be to make additional slices in the roll. Students may suggest more exotic means (for example, use a fiber optic light source connected to a minivideo device to view the roll's interior on a remote screen). If suggestions fall in the latter category, congratulate students for their ingenuity. Ask them to think about how to gain the information required quickly and using simple, available technology. In the end, focus student attention on increasing the number of slices. This requires only a knife and can be done quickly.

6. **Ask the students how many slices would be required to define the dyed region(s) in the roll's interior. What are their considerations in providing an answer to this question?**

   The actual number of slices that the students believe is correct is not the important issue. If students do provide a specific answer, ask them to justify it. It is important for them to understand the following. First, multiple slices *are* required to define the object's properties. The *size* of the slices will determine the resolution used to define the object's properties. Thicker slices will provide less resolution, just as the 3 × 3 probes provided low resolution in Activity 1. Thinner slices will provide greater resolution, just as the 1 × 1 probes did in Activity 1.

7. **Ask students to have their group's Master 2.3 to 2.8 available. Explain that the "level" designation below the grid (Level 1, 2, 3, 4, 5, or 6) on the master indicates the location of a slice through an object.**

   Level 1 is the top slice, followed by 2, 3, 4, 5, and 6 (at the bottom).

8. **Ask students to visualize their pattern in three dimensions by imagining that their shaded pattern represents the top of a stack of gray blocks. Their level is a slice two blocks thick.**

9. **Ask the groups to share their data (that is, the location of the shaded regions) and try to reconstruct the three-dimensional object that has been cut into six slices.**

   Do not provide additional guidance. Give students about five minutes to do this. Students may or may not be able to reconstruct the object in this time.

For those using the **Web version** *of this activity, proceed as follows:*

10. **Were students able to arrive at a solution? What might have made the task of reconstructing the object in three dimensions easier?**

    Students might suggest that a computer could provide the technology to make reconstruction easier.

11. **Have students proceed to the URL *http://science.education.nih.gov/supplements/technology/student*. Students should then click on the link to "Lesson 2—Solution to Probing for Answers." This brings up the unit's desktop, from which students can access this activity.**

12. **Students can enter their data by first selecting a level (1 to 6) and then clicking on the squares they determined to be shaded. The reconstructed object will appear as data are entered.**

    It may be easier and less time consuming for the teacher to enter the data provided by the students.

Content Standard E: Identify a problem or design an opportunity.

Content Standard E: Implement a proposed solution.

Content Standard A: Scientists rely on technology to enhance gathering and manipulating data.

For those using the **print version** *of this activity, proceed as follows:*

10. **Show students a transparency of Master 2.9, *Solution to Probing for Answers*. Were they able to arrive at this solution? What might have made their task easier?**

    Some students do well thinking in three dimensions, and others do not. Many may recognize the need for additional technology, such as a computer and appropriate software, to make the job of reconstruction easier. Even a simple technology, such as wooden blocks or Legos, could have been used to construct a three-dimensional model of the intact object.

Content Standard E: Identify a problem or design an opportunity.

Assessment:
This question allows students to integrate the information they have learned in the first two lessons and refine their understanding of what technology is.

Discussion Question

1. **As a follow-up, ask students, "Have these activities expanded your understanding of technology? If they have, how?"**

   Activity 1 demonstrates the use of multiple probes to achieve different levels of resolution. It also demonstrates that the right tool, in this case a probe of appropriate size, must be selected to solve a problem (resolving the structure of an unknown object). Therefore, students should realize that there is an appropriate technology for a given problem (that is, the right tool for the job). Activity 2 demonstrates that solutions to a problem may involve more than one technology (the use of slices to determine the structure of a three-dimensional object and technologies to collect and analyze the data).

Lesson 2 Organizer: Web Version

Activity 1: *Probing for Answers*

What the Teacher Does	Procedure Reference

State or write on the board, "Technology is a means of extending human potential or of extending human senses."
• Ask students if they agree with this statement.
• Ask students to provide justification for their responses. Can they relate specific technologies to the extension of specific human attributes or senses?
• Ask students to consider technologies that have increased our understanding of living systems.
  o Do they extend any human attributes?
  o If they do, which attributes are extended?
	Pages 57–58
	Steps 1–3

Ask students to focus on technologies (the eye, microscopes, X-ray techniques) that allow us to see biological objects. Ask, • "What technologies would you use to study a whole organism and why?" • "What technologies would you use to study cells and why?" • "What techniques would you use to study molecules and why?" • "Why can't a single technology provide information at all levels of organization of biological organisms?" Introduce the concept of resolution. Ask students what resolution means.	Page 58 Steps 4–6
Tell students that they will investigate resolution. Organize the class into groups of two and then pair two groups. • Arrange seating so that one group sits opposite the other. • Explain that the activity resembles the game Battleship. • Each group's task is to locate and define the shape of an object or objects on the master held by the opposing group. • Give each group a copy of Master 2.1, *Probing for Answers Score Sheet.* • Use a transparency of this master to demonstrate how the activity is done.	Pages 59–60 Steps 7–11 M T

Begin the activity. • Give each group one master selected from Masters 2.3 to 2.8, *Probing for Answers—Levels 1–6*. • Give each group a 3 × 3 probe from Master 2.2, *Probes*. Instruct students to use this probe to locate areas 3 squares by 3 squares that contain the opposing group's shaded object(s). • After five minutes, ask students if they have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s). • Ask students what would help them define the shape and location of the opposing group's shaded object(s). • Give each group a 2 × 2 probe and ask them to refine their search with this probe. • After several minutes, ask students if they believe they now have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s). • Give each group a 1 × 1 probe and ask them to refine their search with this probe. • After several minutes, ask students if they believe they now have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s). Do they need another probe to complete their task? • Have opposing groups confirm that after using the series of three probes, they were able to determine the correct pattern on one another's master. Proceed to discussion questions.	Pages 60–62 Steps 12–20 M

Activity 2: *More Than Meets the Eye*

What the Teacher Does	Procedure Reference
Hold a bread roll into which you have inserted food dye up to the class. • Ask students to describe what they see. • Is there anything about the roll they do not know from just looking at it? • Focus discussion on what is inside the roll and ask students how they would get that information. • Slice the roll to reveal the dye. • Ask students if they feel that they now have complete information about the object. • What additional questions do they have and how could they get the answers? • How many slices are required to define the dyed region(s) in the roll's interior? Focus discussion on resolution.	Pages 63–64 Steps 1–6

Ask students to have their Master 2.3 to 2.8 available. • Explain that the "level" designation on the master indicates the location of a slice through an object (1 at the top to 6 at the bottom). • Ask students to visualize their pattern in three dimensions by imagining that their shaded pattern represents the top of a stack of grey blocks. Their level is a slice two blocks thick. • Ask the groups to share their data (that is, the location of the shaded regions) and try to reconstruct the three-dimensional object that has been cut into six slices. • Ask if students were able to arrive at a solution. What might have made their task easier?	Pages 64–65 Steps 7–10
Have students click on "Lesson 2—Solution to Probing for Answers" and then click on the link to "Solution to Probing for Answers." Have students enter their data to reconstruct the object.	Page 65 Steps 11–12

M = Involves copying a master.

www = Involves using the Internet.

T = Involves using a transparency.

Lesson 2 Organizer: Print Version

Activity 1: *Probing for Answers*

What the Teacher Does	Procedure Reference

State or write on the board, "Technology is a means of extending human potential or of extending human senses."
• Ask students if they agree with this statement.
• Ask students to provide justification for their responses. Can they relate specific technologies to the extension of specific human attributes or senses?
• Ask students to consider technologies that have increased our understanding of living systems.
  o Do they extend any human attributes?
  o If they do, which attributes are extended?
	Pages 57–58
	Steps 1–3

Ask students to focus on technologies (the eye, microscopes, X-ray techniques) that allow us to see biological objects. Ask, • "What technologies would you use to study a whole organism and why?" • "What technologies would you use to study cells and why?" • "What techniques would you use to study molecules and why?" • "Why can't a single technology provide information at all levels of organization of biological organisms?" Introduce the concept of resolution, Ask students what resolution means.	Page 58 Steps 4–6
Tell students that they will investigate resolution. Organize the class into groups of two and then pair two groups. • Arrange seating so that one group sits opposite the other. • Explain that the activity resembles the game Battleship. • Each group's task is to locate and define the shape of an object or objects on the master held by the opposing group. • Give each group a copy of Master 2.1, *Probing for Answers Score Sheet.* • Use a transparency of this master to demonstrate how the activity is done.	Pages 59–60 Steps 7–11 M T

Begin the activity. • Give each group one master selected from Masters 2.3 to 2.8, *Probing for Answers—Levels 1–6*. • Give each group a 3 × 3 probe from Master 2.2, *Probes*. Instruct students to use this probe to locate areas 3 squares by 3 squares that contain the opposing group's shaded object(s). • After five minutes, ask students if they have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s). • Ask students what would help them define the shape and location of the opposing group's shaded object(s). • Give each group a 2 × 2 probe and ask them to refine their search with this probe. • After several minutes, ask students if they believe they now have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s). • Give each group a 1 × 1 probe and ask them to refine their search with this probe. • After several minutes, ask students if they believe they now have enough information to specify the exact shape(s) and location(s) of the opposing group's shaded object(s). Do they need another probe to complete their task? • Have opposing groups confirm that after using the series of three probes, they were able to determine the correct pattern on one another's master. Proceed to discussion questions.	Pages 60–62 Steps 12–20 M

Activity 2: *More Than Meets the Eye*

What the Teacher Does	Procedure Reference
Hold a bread roll into which you have inserted food dye up to the class. • Ask students to describe what they see. • Is there anything about the roll they do not know from just looking at it? • Focus discussion on what is inside the roll and ask students how they would get that information. • Slice the roll to reveal the dye. • Ask students if they feel that they now have complete information about the object. • What additional questions do they have and how could they get the answers? • How many slices are required to define the dyed region(s) in the roll's interior? Focus discussion on resolution.	Pages 63–64 Steps 1–6

Ask students to have their Master 2.3 to 2.8 available. • Explain that the "level" designation on the master indicates the location of a slice through an object (1 at the top to 6 at the bottom). • Ask students to visualize their pattern in three dimensions by imagining that their shaded pattern represents the top of a stack of grey blocks. Their level is a slice two blocks thick. • Ask the groups to share their data (that is, the location of the shaded regions) and try to reconstruct the three-dimensional object that has been cut into six slices. • Show students a transparency of Master 2.9, *Solution to Probing for Answers.* • Ask if students were able to arrive at this solution. What might have made their task easier?	Pages 64–65 Steps 7–10 M T

M = Involves copying a master.

T = Involves using a transparency.

Lesson 3
Explore
Explain
Elaborate

Putting Technology to Work

At a Glance

Overview

This lesson consists of a single activity with three parts in the Web version and four parts in the print version. It will take two days to complete. The lesson provides an opportunity for students to investigate some technologies that have advanced our understanding of cellular and molecular biology. Probe size, resolution, and using the right tool for the job are emphasized. Students are presented with a fictitious scenario involving the discovery of a muscle-wasting disease. As members of a medical and scientific team, they must choose a technology to use—light microscopy, transmission electron microscopy, cryo-electron microscopy, or X-ray crystallography—to investigate the disease. They answer questions such as, What is the infectious agent, how does the infectious agent cause disease, and is there a drug to treat or prevent the disease?

Major Concepts

Technologies that differ in their resolving capabilities provide different information about the structure of an object. Solving a problem requires an appropriate technology or series of technologies. Technology provides valuable tools for solving scientific problems relevant to human health.

Objectives

After completing this lesson, students will

- be able to explain the use of technologies based on their resolving power,
- be able to explain how technologies are used to solve scientific and health-related problems,
- be able to explain the concept of using the right tool for the job, and
- be able to develop a multistep research plan in which hypotheses are formulated, data are gathered and interpreted, and new questions are asked.

Teacher Background

See the following sections in Information about Using Technology to Study Cellular and Molecular Biology:

3 Scale and Resolution *(pages 24–26)*

4 Major Techniques in the Study of Cellular and Molecular Biology *(pages 26–35)*

In Advance

Web-Based Activities

Activity	Web Version
1	Yes

Photocopies

For classrooms using the Web version of this activity:	• Master 3.1, *Memo from the Director, Global Science and Health Organization,* 1 copy per group • Master 3.2, *Research Plan*, 1 copy per student and 1 transparency • Master 3.3, *Example of a Research Plan*, 1 transparency • Master 3.4, *Drug Discovery Evaluation Form*, 1 copy per student
For classrooms using the print version of this activity:	• Master 3.1, *Memo from the Director, Global Science and Health Organization*, 1 copy per group • Master 3.2, *Research Plan*, 1 copy per student or 1 transparency for class • Master 3.3, *Example of a Research Plan*, 1 transparency • Master 3.5, *Available Technologies*, 1 transparency • Master 3.6, *Science Reference Manual*, 1 copy per group • Master 3.7, *Muscle Protein Structures Determined by X-Ray Crystallography*, 1 copy per group or 1 transparency for class

Materials

Activity 1	none required

Preparation

For classrooms using the Web version *of this activity:*
Verify that computer lab is reserved for two consecutive class periods or that classroom computers are ready to use. To save time, have computers at the URL *http://science.education.nih.gov/technology/student*. This is a main menu page from which this activity can be accessed.

For classrooms using the print version *of this activity:*
No preparations needed.

Procedure

For classrooms using the Web version *of this activity.*

Teacher note: This activity allows students to enter a virtual laboratory in which they use microscopic techniques and X-ray crystallography to solve a problem. The activity requires students to

view and interpret data. An essential part of it is having students develop a logical research plan based in part on what they learned earlier in this module about scale and resolution. They should formulate hypotheses that can be tested with the technologies available to them.

Part 1, Solving the Problem

1. **Divide the class into groups of two students each, and give each group a copy of Master 3.1, *Memo from the Director, Global Science and Health Organization.***

2. **Ask students to read the memo and note the questions they are instructed to answer.**

   This memo also appears when students access the activity on the Web. Students can retain the printed memo to remind themselves of the questions they are to answer.

3. **Explain that students will begin by formulating a research plan. They will develop hypotheses that can be tested in their virtual laboratory.**

   If necessary, remind students that hypotheses are statements that predict a result and are testable experimentally.

4. **Ask students to proceed to *http://science.education.nih.gov/supplements/technology/student*. They should click on the link to "Lesson 3—Putting Technology to Work." This brings up the unit's desktop, from which this activity can be accessed.**

   After clicking on the activity link on the desktop, the memo from the director appears. After students close the memo, each of the four available technologies is highlighted. **Note:** Students should not yet click on a technology.

5. **Explain that students have resources available to them, including various technologies and reference materials. Ask students to click on the link to "Reference Manual."**

   Briefly review the contents of the Reference Manual with the students.

   Tip from the field test: Field-testing has indicated that it is very useful for teachers to introduce students to the Science Reference Manual early in this activity (see Teacher note 1 on page 79). This resource contains valuable information to help students formulate their hypotheses, including the sizes of biological structures and resolution limits of various technologies, as well as details about

unfamiliar technologies, blood cells, muscle cells, and pathogens and how they cause disease. At a minimum, you should introduce students to the table of contents of the Science Reference Manual, point out which topics are links to more information, and use one link to show students the kind of information provided.

6. **Ask students how they will begin their studies. What should they do first? Encourage student participation and accept all responses.**

   Teacher note: Even though students are in pairs, work with the class as a whole through Step 15 to help them understand the process.

   This question is purposely vague. Its intent is to engage the students and initiate creative thinking. Student responses may vary considerably. Some students may suggest beginning at the lowest level of resolution, the eye, and visually confirming the presence of ill individuals. They may suggest talking with healthy and ill individuals to gain clues about the nature of the disease. They may want more details about symptoms. Indicate to students that while gaining additional information by talking with affected and unaffected individuals might be helpful, there is no time to travel. They need to get down to business and begin investigating the issues raised in the director's memo.

7. **Direct students to the first question in the director's memo. Choosing from the available technologies and using tissue samples from affected and unaffected individuals, how can they confirm the presence of disease at the cellular level in the affected population?**

   Students have muscle and blood samples available for study. Students should reason that light microscopy can be used to look for the presence of abnormal muscle cells in affected individuals. Unaffected individuals should have normal muscle cells. Students should provide a reason for wanting to look at any other tissue samples.

8. **Ask students, "Why would you use light microscopy to confirm the presence of disease?"**

   Students should know that cells are too small to be seen by the naked eye, although they can be seen easily with a light microscope. If necessary, ask students to think about the information on Master 1.1, *Searching for Scale* (the size of a cell) and what they discovered in Lesson 2, Activity 1: *Probing for Answers* (start with the largest probe, in this case visible light).

9. **After deciding on a starting point (light microscopy), students should begin constructing their detailed research plan. Give each student a copy of Master 3.2, *Research Plan*.**

   Master 3.2 presents an example of how a research plan can be organized. It is important for students to see how information flows as an investigation proceeds and how what is done at one step depends on results from previous steps.

10. **Use the transparency of Master 3.2 to demonstrate how the research plan is constructed. Use Master 3.3, *Example of a Research Plan*, as your guide.**

11. **In the space next to the statement, "To answer the question," write the question, Is there evidence of disease at the cellular level (in muscle cells)? Ask students to help you determine which technology to use to answer this question.**

    Students should choose to begin their studies with light microscopy to look for the presence of abnormal cells in the muscle tissue of affected individuals. Write this response in the space next to the statement, "I will use this technology."

12. **Ask students to respond to the statement, "I chose this technology because."**

    Students should have reasoned that cells are too small to be seen with the naked eye but can be seen easily using a light microscope. In other words, the resolution of a light microscope is sufficient to see individual cells. Record the response on the transparency.

13. **Ask students to state a hypothesis.**

    There is (or is not) evidence of disease in muscle cells.

14. **Ask students what two results they would expect.**

    Either abnormal muscle cells will be seen in affected individuals or they will not. Record this response on the transparency.

15. **Ask students what question they would answer next if they observe abnormal muscle cells in affected individuals.**

    They would proceed to Question 2 on Master 3.1, *Memo from the Director*, Is the disease caused by an infectious agent? Record this response on the transparency.

16. **Ask students what question they would answer next if they do not observe abnormal muscle cells in affected individuals.**

NSES

Content Standard A: Identify questions and concepts that guide scientific investigations.

Content Standard A: Design and conduct a scientific investigation.

There is no single response to this question. Students can use their imagination.

Encourage students to use the Science Reference Manual to learn about muscle and blood cells. Examples of normal muscle and blood cells are included in the reference material. Information about the size of cells, bacteria, and viruses is also provided, as well as the various technologies students will investigate in this activity.

17. **Ask students to complete all tasks except those dealing with discovery of a drug to treat the disease (Question 6 on Master 3.1, *Memo from the Director, Global Science and Health Organization*).**

18. **Instruct students to begin their studies. They should make careful observations at each step and record all of their observations. They should follow their research plan.**

    Circulate among groups as students work. Ensure that students are proceeding according to a rational plan they have developed. You may want to quiz students about why they selected a specific technology, what they hoped to see, how they interpret what they did see, or why a technology is appropriate for solving a specific problem.

Teacher notes:

1. Selecting a technology activates a short animation. For example, after clicking on the light microscope, the animation changes from a view of the whole instrument to the view students would have looking through the eyepiece. Then, a small window opens over an interactive screen. This window contains information about the samples available for investigation, such as what the sample is (for instance, tissue or protein), and the source of the sample (that is, from a person with the disease or from an unaffected individual). Samples are coded, and students should record the coding information.

2. The light microscope and the transmission electron microscope are interactive. Students should begin by selecting a sample and adjusting the brightness by moving the brightness slider. Magnification of the sample can be changed. Students can move most cell and tissue images up and down and to the left and right. Students may take a snapshot of a field they are viewing by clicking on the "View Snapshots." Clicking on an individual snapshot produces a larger image that can be compared with another on-screen image (that is, an image on the microscope or an image in the Reference Manual). The "View Snapshot" window may be moved to allow easier comparison of images. Up to 12 snapshots may be stored.

3. Using the cryo-EM, students should click on "Affected" and "Unaffected." They should record their observations of what appears in the

electron microscope (left monitor) and in the three-dimensional reconstruction (right monitor).

4. After clicking on "X-ray Crystallography," students see a detailed animation of the process. We indicate that the data were obtained from three different orientations of the protein crystal, which is far fewer than the thousands of different orientations actually used in a research laboratory. Students begin by making observations of the X-ray crystallography patterns that appear on screen. All that students—or scientists, for that matter—can judge at this point is that the patterns for the affected and unaffected proteins are different from one another for each orientation. Making sense of these data requires processing by high-speed computers using specialized software. Finally, students compare three-dimensional models of the affected and unaffected proteins. They should use the slider to rotate the proteins and record their observations of the differences and similarities of the proteins' structures.

19. **When students have completed their work and answered Questions 1 through 5 on Master 3.1, *Memo from the Director, Global Science and Health Organization*, reconvene the class.**

20. **One at a time, have groups share their findings with the rest of the class.**

    Presentations need not be long. However, students should demonstrate an understanding of scale, resolution, and selecting the right tool for the job. Members of each group should share the responsibilities of presenting the group's information. Students should be encouraged to question the hypotheses, research plans, and interpretations of others. Remind students that science is a collaborative process in which scientists must be able to support their ideas.

Teacher notes:

1. The Science Reference Manual contains information that is very helpful to students, and they should consult it early in their investigations. For instance, students can view light micrographs of normal muscle. They will also find information on two common pathogens, bacteria and viruses, thus limiting the pathogens they search for. Additionally, key information about technologies is presented.

2. Students should reason that light microscopy can be used to look for the presence of abnormal muscle cells in affected individuals. Students generally know that cells are too small to be seen by the naked eye, although they can be seen easily with a light microscope. If necessary, ask students to think about the information on Master 1.1, *Searching for Scale*, (the size of cell) and what they discovered in Lesson 2, Activity 1: *Probing for Answers* (start with the largest probe, in this case visible light). In this activity, unaffected individuals have normal muscle cells.

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Content Standard A: Formulate and revise scientific explanations and models using logic and evidence.

Content Standard A: Recognize and analyze alternative explanations and models.

Content Standard A: Communicate and defend a scientific argument.

Individuals susceptible to disease have abnormal muscle cells.

3. The Science Reference Manual lists two common pathogens: bacteria and viruses. Students should focus on the 10- to 100-fold difference in size between bacteria and viruses. Light microscopy can be used to resolve bacteria, but not viruses. Students should understand that they are following a plan analogous to the one developed in Lesson 2. They are starting with the largest probe available (visible light) to find out about the largest possible structures that can be resolved.

4. No bacteria are visible in either muscle or blood samples. Therefore, students should use transmission electron microscopy to see whether viruses are present in any of the tissue samples. Viruses are readily visible with this technique, which uses a probe (electrons) that is smaller than the probe they used initially (visible light).

5. Transmission electron microscopy demonstrates the presence of viruses in blood and muscle tissue samples from one affected and one unaffected individual. A second set of unaffected blood and muscle samples does not contain viruses. This observation is a key finding for this activity, although it may be confusing to some students. How do students interpret the presence of virus and the absence of disease? How might this relate to how the virus produces disease in susceptible individuals? They can consult their Science Reference Manual for helpful information.

A possible reasoned scenario is 1) virus is present in muscle tissue of both affected and unaffected individuals because the virus binds to a protein receptor in that tissue, 2) the virus nucleic acid codes for a protein produced by the muscle cells, 3) the virus protein binds to a key muscle protein in cells of affected individuals, which causes the disease, 4) the virus protein does not bind to the muscle protein in cells of unaffected individuals, 5) the *affected* muscle protein has a different structure from the unaffected protein, and 6) this difference in structure allows the *affected* muscle protein to interact with the virus protein.

6. On the basis of the scenario presented above, a hypothesis might be as follows: the structure of the affected muscle protein is different from that of the unaffected muscle protein. An extension of this hypothesis is that the virus protein binds to the affected muscle protein and not the unaffected muscle protein because of differences in structure between the two muscle proteins.

7. On the basis of the scenario presented above, students can use cryo-EM to generate a three-dimensional reconstruction of the virus attached to the muscle to see whether the virus attaches to affected muscle fibers and not unaffected muscle fibers, and they can use X-ray crystallography to compare the structures of affected and unaffected muscle proteins.

8. To students—and to trained scientists, as well—the X-ray crystallography patterns are a collection of spots that do not themselves present a clear and obvious picture of a molecule's structure. Students can note that the patterns differ from one another in spot location and intensity. They should understand that each pattern is unique because the structure being investigated is unique; that is, different patterns are produced both by different orientations of the same molecule and by different molecules. Students should also see the value of computer technology in providing three-dimensional molecular structure from a series of X-ray crystallography patterns. Please note that many more than three X-ray crystallography patterns are required to produce a three-dimensional structure. The process has been simplified for this activity.

9. Students should evaluate how the structure of the affected muscle protein compares with the unaffected muscle protein. The only visible difference between the two proteins is seen in the view along the z-axis (that is, from the top looking down). The affected muscle protein has an opening that is not present in the unaffected muscle protein.

Part 2, Applying Technology . . . Again

1. **On behalf of the Global Science and Health Organization, thank students for their efforts. They have provided answers to some important questions. However, one very important question remains: Is there a drug to treat or prevent the disease?**

2. **Ask students how the structural data on the affected and unaffected muscle proteins, obtained by X-ray crystallography, suggest a way that the virus could cause the disease.**

   Accept all responses. It is possible that the affected muscle protein can interact with the virus protein because its structure is different from that of the unaffected muscle protein. Students might wonder how this interaction could occur. They might speculate that the virus protein interacts with parts of the affected muscle protein around the opening that exists. It also may be that the virus protein interacts with some other region of the affected muscle protein. Alternatively, students may hypothesize that the virus causes the hole in the affected muscle protein. In other words, this action of the virus produces a muscle protein of changed structure and, therefore, changed function.

3. **How might a drug be used to treat the disease?**

   This is another opportunity for students to relate structure to function. They might reason that the affected muscle protein interacts with the virus protein and not the unaffected muscle protein because the two muscle proteins have different structures. This

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Content Standard A: Scientists conduct investigations for a wide variety of reasons, such as to discover new aspects of the natural world, to explain observed phenomenon, or to test conclusions of prior investigations or predictions of current theories.

difference appears to be characterized primarily by an opening in the affected muscle protein. Therefore, perhaps a drug can be developed to change the affected muscle protein's structure to one more like the unaffected muscle protein. A simple possibility is to develop a drug to close the opening. Students may suggest other possibilities as well. Do not limit their thinking or try to guide the discussion one way or another.

4. **Direct student groups to their computers. Tell them that the director of the Global Science and Health Organization has requested that they evaluate four new drugs that are believed to have potential to treat the disease.**

5. **Give each student a copy of Master 3.4, *Drug Discovery Evaluation Form*. They should use this form to record their observations and interpretations.**

6. **Ask students to click on the link "Drug Discovery Laboratory" on the unit's desktop.**

   A memo appears that gives students the instructions for this activity. Students compare the unaffected muscle protein with a complex formed by combining a drug molecule with the affected muscle protein. Four different drug molecules are available. When students close the memo, a short animation comes on that leads to a screen on which appear the unaffected protein, the affected protein, and the four drug molecules. Students can make observations about their structures. Clicking on a drug molecule attaches that drug to the affected protein. Students should use the slider to rotate the two proteins and compare their structures.

   The instructions to students are purposely general. Students should conclude that the drugs have been designed such that they either do or don't convert the structure of the affected muscle protein to one more like the unaffected protein. Students will observe that none of the drugs interacts with the affected muscle protein to form a structure that is exactly the same as the unaffected muscle protein. This, too, is purposeful and is intended to stimulate student thinking.

   Depending on the class time you have available, you can assign groups all four molecules to evaluate or a limited number of molecules (one or two) to evaluate.

Part 3, Wrapping It Up

1. **Reconvene the class. Ask groups to share their drug evaluations. What were the drugs apparently designed to do? Do any drugs show promise for treating the disease?**

This discussion allows students to share thoughts about what they have done. They should focus on results and interpretations. Students should understand that the path to solving a scientific problem is long and complex and that technology plays a key role in the process. They also come to realize that there are not always neat solutions to problems.

2. **Instruct students to prepare a report that summarizes their work.**

   They are to present their group's work, from development of a research plan to drug discovery. It is acceptable for students to add their own touches to the group effort, based on class discussions and further reflection. They should focus on
   - justifying their choice of technology to solve specific problems,
   - demonstrating an understanding of specimen size and resolution, and
   - indicating a logical flow for using technologies of increasing resolution to solve problems.

Content Standard A: Formulate and revise scientific explanations and models using logic and evidence.

For classrooms using the **print version** *of this activity*

Teacher note: The print version of this activity is a "thought" activity. It does not make use of the graphics found in the Web activity, since these graphics do not always reproduce well. This version of the activity is more open-ended than the Web version. It allows students more latitude in formulating a research plan, since they are not restricted by available resources. Most important in this activity is the students' reasoning. Why do they propose to use a given technology? What results do they expect? How will this lead them to the next step in their plan? Students work in groups to increase interaction and collaboration.

Part 1, What Is It?

1. **Divide the class into groups of three or four students each, and give each group a copy of Master 3.1, *Memo from the Director, Global Science and Health Organization*.**

2. **Ask students to read the memo.**

3. **Show students the transparency of Master 3.5, *Available Technologies*.**

   Tell students that to help them answer the questions raised by the director of the Global Science and Health Organization, the following technologies are available: observation by naked eye, light microscopy, transmission and cryo-electron microscopy, and X-ray crystallography. Remind them (as stated in the memo) that tissue samples from affected and unaffected individuals will be available.

Content Standard A:
Design and conduct a scientific investigation.

4. **Give each group a copy of Master 3.6, *Science Reference Manual*. Explain to students that as scientists, they need reference materials to help them develop a logical and realistic research plan.**

   Tip from the field test: Field-testing indicated that it is very useful for teachers to introduce students to the Science Reference Manual early in this activity (see Teacher note 1 on page 79). This resource contains valuable information to help students formulate their hypotheses, such as sizes of biological structures and resolution limits of various technologies. It also contains information about unfamiliar technologies, such as X-ray crystallography, as well as about blood cells, muscle cells, and pathogens and how they cause disease. At a minimum, you should introduce students to the Table of Contents of the Science Reference Manual and point out the information provided there.

5. **Ask students how they will begin their studies. What should they do first? Encourage student participation and accept all responses.**

   Teacher note: Even though students are in smaller groups of three or four, work with the class as a whole through Step 14 to help them understand the process they will follow.

   This question to students is purposely vague. Its intent is to engage the students and their imagination. Responses may vary considerably. Some students may suggest beginning at the lowest level of resolution, the eye, and visually confirming the presence of ill individuals. They may suggest talking with healthy and ill individuals to gain clues about the nature of the disease. They may want more details about symptoms. Indicate to students that while gaining additional information by talking with affected and unaffected individuals might be helpful, there is no time to travel. They need to get down to business and begin investigating the issues raised in the director's memo.

6. **Direct students to the first question in the director's memo. Choosing from the available technologies, and using tissue samples from affected and unaffected individuals, how can they confirm the presence of disease at the cellular level in the affected population?**

   If students ask what tissue samples are available, ask them to consider which tissue samples they would want and why. Students should reason that light microscopy can be used to look for the presence of abnormal muscle cells in affected individuals. Unaffected individuals should have normal muscle cells. Students should provide a reason for wanting to look at any other tissue samples.

7. **Ask students, "Why would you use light microscopy to confirm the presence of disease?"**

   Students should know that cells are too small to be seen by the naked eye, although they can be seen easily with a light microscope. If necessary, ask students to think about the information on Master 1.1, *Searching for Scale* (the size of a cell) and what they discovered in Lesson 2, Activity 1: *Probing for Answers* (start with the largest probe, in this case visible light).

8. **After deciding on a starting point (light microscopy), students should begin to create their detailed research plan. Master 3.2, *Research Plan*, presents an example of how a research plan can be organized.**

   Either give each student a copy of Master 3.2 or make a transparency of Master 3.2 to show the class. It is important for students to see how information flows as an investigation proceeds and how what is done at one step depends on results from previous steps. The research plan is constructed as a modified decision tree: if I see (result 1), I will do (next task); or, if I see (result 2), I will do (next task).

9. **Use the transparency of Master 3.2, *Research Plan*, to demonstrate how the research plan is constructed. Use Master 3.3, *Example Research Plan*, as your guide.**

10. **Begin by writing the question, Is there evidence of disease at the cellular level (in muscle cells)?, in the space next to the statement, "To answer the question." Ask students to help you determine which technology to use to answer this question.**

    Students should begin their studies with light microscopy to look for the presence of abnormal cells in the muscle tissue of affected individuals. Write this response in the space next to the statement, "I will use this technology."

11. **Ask students to respond to the statement, "I chose this technology because."**

    Students should reason that cells are too small to be seen with the naked eye but can be seen easily using a light microscope. In other words, the resolution of a light microscope is sufficient to see individual cells. Record the response on the transparency.

12. **Ask students to state a hypothesis.**

    There is (or is not) evidence of disease in muscle cells.

13. **Ask students what two results they would expect.**

    Either abnormal muscle cells will be seen in affected individuals or they will not. Record this response on the transparency.

14. **Ask students what question they would answer next if they observe abnormal muscle cells in affected individuals.**

    Students would proceed to Question 2 on Master 3.1, *Memo from the Director*, Is the disease caused by an infectious agent? Record this response on the transparency.

15. **Ask students what question they would answer next if they do not observe abnormal muscle cells in affected individuals.**

    There is no single response to this question. Students can use their imagination.

16. **Inform students that they are ready to begin their studies. They should create their research plans in a manner similar to that demonstrated.**

17. **Inform the class that results indicate the presence of abnormal muscle cells in tissue samples from affected individuals but not in unaffected individuals. First, they will address the question of whether or not the disease is caused by an infectious agent.**

    Students now begin working in smaller groups.

18. **The Science Reference Manual lists two common *pathogens*: bacteria and viruses. How could they identify one or the other as a potential cause of the disease (that is, as being present in affected individuals and not present in unaffected individuals) using the technologies available to them?**

    They should name the technology they would use, justify their choice based on the size of the objects they are looking for and the resolving power of the technology, and indicate possible results and what their next step would be. Allow groups no more than five minutes to formulate their plan.

19. **Ask a group to present its research plan very briefly.**

    Students should focus on the 10- to 100-fold difference in size between bacteria and viruses. Light microscopy can be used to resolve bacteria but not viruses. Students should understand that they are following a plan analogous to that developed in Lesson 2. They start with the largest probe available (visible light) to find out about the largest possible structures that can be resolved.

20. **Ask whether any groups have a different research plan.**

    Ask groups with a different research plan to make a brief presentation. Use class discussion to resolve differences or reinforce similarities.

21. **Inform the class that light microscopy did not demonstrate the presence of any structures resembling bacteria in tissue samples from affected or unaffected individuals. On the basis of this result, students should now formulate the next step in their research plan.**

    As before, students should name the technology they would use, justify their choice on the basis of the size of the objects they are looking for and the resolving power of the technology, and indicate possible results and what their next step would be. Allow groups two to three minutes to confirm their plan.

Content Standard A: Formulate and revise scientific explanations and models.

22. **Ask a group to present its research plan very briefly.**

    Students should use transmission electron microscopy to see whether viruses are present in any of the tissue samples. Viruses are readily visible with this technique, which uses a probe (electrons) that is smaller than the probe they used initially (visible light). Ask students to justify any other approach they suggest.

23. **Ask whether any groups have a different research plan.**

    Ask groups with a different research plan to make a brief presentation. Use class discussion to resolve differences or reinforce similarities.

Part 2, How Does It Work?

1. **Inform the class of the following results:**
   - **transmission electron microscopy demonstrated the presence of viruses in blood and muscle tissue samples from *both* affected and unaffected individuals,**
   - **no other tissue samples contained viruses,**
   - **there were more viruses in muscle of affected people than in unaffected people, and**
   - **the viruses appeared to be associated with actin filaments in the muscle.**

2. **Ask students to consider these results as they develop their plan to answer Questions 4 and 5 on the director's memo (Master 3.1). For instance,**
   - **How do students interpret the presence of virus and the absence of disease?**
   - **How might this relate to how the virus produces disease in susceptible individuals?**

This may be a tough issue for students to deal with. It is not important for them to come up with our scenario. It is important for them to reason properly and use the available technologies to solve whatever problem they perceive exists. *They should consult their Science Reference Manuals for helpful information.*

A possible reasoned scenario is 1) virus is present in muscle tissue of both affected and unaffected individuals because the virus binds to a receptor in that tissue, 2) the virus nucleic acid codes for a protein produced by the muscle cells, 3) the virus protein binds to a key muscle protein in cells of affected individuals, which causes the disease, 4) the virus protein does not bind to the muscle protein in cells of unaffected individuals, 5) the *affected* muscle protein has a different structure from the *unaffected* protein, and 6) this difference in structure allows the *affected* muscle protein to interact with the virus protein.

3. **Ask groups to form a hypothesis based on their assessment of the data presented in Step 1 of Part 2.**

   On the basis of the sample scenario presented in Part 2, Step 2, one hypothesis might be as follows: the structure of the affected muscle protein is different from that of the unaffected muscle protein. A related hypothesis might be that the virus protein binds to the affected muscle protein and not the unaffected muscle protein because of differences in structure between the two muscle proteins. Another hypothesis is that the virus can attach to affected muscle fibers and not to unaffected muscle fibers. There are many possible hypotheses. It is important that each student hypothesis be a testable statement that predicts a result.

4. **Ask groups to formulate a plan to test their hypothesis. They should use only the techniques available to them.**

   On the basis of the sample scenario presented in Part 2, Step 2, students might propose to do the following:
   - use cryo-EM to generate a three-dimensional reconstruction of the virus attached to the muscle to see whether the virus attaches to affected muscle fibers and not unaffected muscle fibers,
   - use cryo-EM to produce three-dimensional reconstructions of both the affected and unaffected muscle proteins to look for differences in structure between the two,
   - use X-ray crystallography to compare the structures of affected and unaffected muscle proteins, or
   - use either cryo-EM or X-ray crystallography to look at the structure of any virus-muscle protein combination that might form (that is, a virus protein-affected muscle protein combination or a virus protein-unaffected muscle protein combination).

Students might come up with other possibilities depending on the hypothesis they formulate.

5. **Ask a group to present its hypothesis and research plan.**

   Members of each group should share the responsibilities of presenting the group's information. Students should be encouraged to question the hypotheses and research plans developed by others. Remind students that science is a collaborative process in which scientists must be able to support their ideas.

Content Standard A: Communicate and defend a scientific argument.

6. **Ask whether any groups have a different hypothesis or research plan.**

   Ask groups with a different research plan to make a brief presentation. Use class discussion to resolve differences or reinforce similarities. On the basis of feedback from their fellow scientists, groups should be allowed to revise their hypotheses and research plans.

Content Standard A: Recognize and analyze alternative explanations and models.

Part 3, What Can We Do about It?

1. **Thank students, on behalf of the Global Science and Health Organization, for their efforts so far. They must now think about developing a drug to treat this newly discovered disease.**

2. **If the hypothesis students developed in Part 2 of this activity (about how the virus might produce disease) is supported by experimental data, how could students use a drug to treat the disease?**

   Even though students are still in groups, use this as an opportunity for class discussion. Accept all responses. This question is intentionally vague to stimulate student thinking. If students do not understand the concept of drug targeting (that is, designing a drug to interact specifically with another molecule, such as a host protein or a molecule produced by a pathogen), direct them to review the final item in Master 3.6, *Science Reference Manual*. The drug-specific molecule can be one associated with the pathogen, such as a bacterial or viral surface protein, or a protein produced by the pathogen. Alternatively, the drug-specific molecule can be one associated with the host, such as a receptor for the pathogen, or a molecule with which a pathogen-produced substance interacts.

3. **Tell students that new data have been obtained. Provide each group with a copy of Master 3.7, *Muscle Protein Structures Determined by X-Ray Crystallography*. Alternatively, use a transparency of this master for the class.**

4. **Inform the class that the director of the Global Science and Health Organization wants them to evaluate these structures with**

their fellow scientists (the other group members) and answer a series of questions, which you will write on the board.

- **How does the structure of the affected muscle protein compare with the unaffected muscle protein? Are there differences?**

  The one difference between the two proteins is seen in the view along the z-axis. The affected muscle protein has an opening that is not present in the unaffected muscle protein.

- **Do these results support a way that the virus could cause the disease?**

  They could. It is possible that the affected muscle protein can interact with the virus protein because its structure is different from that of the unaffected muscle protein. Students might wonder how this interaction could occur. They might speculate that the virus protein interacts with parts of the affected muscle protein around the opening that exists. It may also be that the virus protein interacts with some other region of the affected muscle protein.

- **On the basis of these results, what approach might be taken to develop a drug to treat the disease?**

  This is another opportunity for students to relate structure to function. They might reason that the affected muscle protein interacts with the virus protein and not the unaffected muscle protein because the two muscle proteins have different structures. This difference appears to be characterized primarily by an opening in the affected muscle protein. Therefore, perhaps a drug can be developed to change the affected muscle protein's structure to one more like the unaffected muscle protein. A simple possibility is to develop a drug to close the opening. Students may suggest other possibilities as well. Accept any response that students can justify.

- **Using the technologies available, how could potential drugs be tested for effectiveness before using them to treat humans?**

  Responses will depend on the approach taken. For example, X-ray crystallography would be an obvious choice for students who want to demonstrate that a drug has returned the structure of the affected muscle protein to that of the unaffected muscle protein. Accept all responses as long as students justify their use.

5. **Allow groups 10 to 15 minutes to work on their responses. After this time, reconvene the class and ask each group to present their answers.**

Part 4, This, Too, Is What Science Is All About

1. **Remind students that reporting their results is also an important part of doing science. That is what they must do now.**

2. **Instruct students to prepare a report that summarizes the work done within their group.**

   Students are to present all of their group's work, from development of a research plan to drug discovery. It is acceptable, based on class discussions and further reflection, to add their own touches to the group effort. Student reports should
   - focus on justifying their choice of technology to solve specific problems,
   - demonstrate an understanding of specimen size and resolution, and
   - indicate a logical flow in which they use technologies of increasing resolution to solve problems.

Content Standard A: Scientists conduct investigations for a wide variety of reasons, such as to discover new aspects of the natural world, to explain observed phenomena, or to test conclusions of prior investigations or predictions of current theories.

Lesson 3 Organizer: Web Version

Activity 1: *Putting Technology to Work*

What the Teacher Does	Procedure Reference
Part 1, Solving the Problem	
Divide the class into groups of two. • Give each group a copy of Master 3.1, *Memo from the Director, Global Science and Health Organization*. • Ask students to read the memo. • Explain that they will begin by formulating a research plan. • Have students access the activity and click on the link to the reference manual. • Briefly review the contents of the reference manual.	Pages 75–76 Steps 1–5 M WWW
Help students develop a research plan. • Ask students how they would begin their studies. • Guide students to the use of light microscopy to confirm the presence of disease at the cellular level in affected people. • Give each student a copy of Master 3.2, *Research Plan*. • Use a transparency of Master 3.2 to demonstrate how a research plan is developed. • With student input, fill in the required information on the transparency. Use Master 3.3, *Example of a Research Plan*, as a guide. • In the space next to the statement, *To answer the question*, write the question, Is there evidence of disease at the cellular level (in muscle cells)? Ask students to help you determine which technology to use to answer this question. • Ask students to respond to the statement, I chose this technology because. • Ask students to state a hypothesis. • Ask students what two results they would expect. • Ask students what question they would answer next if they do not observe abnormal muscle cells in affected individuals.	Pages 76–78 Steps 6–16 WWW M T

Instruct students to begin their studies. They should construct their research plans in a manner similar to that demonstrated. They should complete all tasks except the one dealing with drug discovery (Question 6 on Master 3.1, *Memo from the Director, Global Science and Health Organization*). Have groups share their findings.	Pages 78–79 Steps 17–20
Part 2, Applying Technology . . . Again	
Remind students of the final question to be answered: Is there a drug to treat or prevent the disease?	Page 81 Step 1
Ask students, • how the structural data on the affected and unaffected muscle proteins, obtained by X-ray crystallography, suggest a way that the virus could cause the disease and • how a drug might be used to treat the disease.	Pages 81–82 Steps 2–3
Direct students to computers. • Tell students that they are to evaluate four new drugs that are believed to have potential to treat the disease. • Give each student a copy of Master 3.4, *Drug Discovery Evaluation Form*, on which they should record their observations and interpretations. • Ask students to click on the link for the Drug Discovery Laboratory on the unit's desktop and complete the activity.	Page 82 Steps 4–6
Part 3, Wrapping It Up	
Reconvene the class. Ask groups to share their drug evaluations. • What were the drugs apparently designed to do? • Do any drugs show promise for treating the disease?	Pages 82–83 Step 1
Instruct students to prepare a report that summarizes their work.	Page 83 Step 2

M = Involves copying a master.

T = Involves using a transparency.

www = Involves using the Internet.

Lesson 3 Organizer: Print Version

Activity 1: *Putting Technology to Work*

What the Teacher Does	Procedure Reference
Part 1, What Is It?	
Divide the class into groups of three or four. • Give each group a copy of Master 3.1, *Memo from the Director, Global Science and Health Organization*. • Ask students to read the memo. • Show students the transparency of Master 3.5, *Available Technologies*. • Give each group a copy of Master 3.6, *Science Reference Manual*.	Pages 83–84 Steps 1–4 M T
Ask students how they will begin their studies. Direct attention to the first question on the director's memo. Ask, • "Choosing from the available technologies and using tissue samples from affected and unaffected individuals, how can you confirm the presence of disease at the cellular level in the affected population?" • "Why would you use light microscopy to confirm the presence of disease?"	Pages 84–85 Steps 5–7
After deciding on a starting point, students should begin constructing their research plan. • Use the transparency of Master 3.2, *Research Plan*, to demonstrate how the research plan is constructed. • With student input, fill in the required information on the transparency. Use Master 3.3, *Example of a Research Plan*, as a guide. • In the space next to the statement, *To answer the question*, write the question, Is there evidence of disease at the cellular level (in muscle cells)? Ask students to help you determine which technology to use to answer this question. • Ask students to respond to the statement, I chose this technology because. • Ask students to state a hypothesis. • Ask students what two results they would expect. • Ask students what question they would next answer if they do not observe abnormal muscle cells in affected individuals.	Pages 85–86 Steps 8–16 M T

Inform the class that results indicate the presence of abnormal muscle cells in tissue samples from affected individuals but not in unaffected individuals. • The class will first address the question of whether or not the disease is caused by an infectious agent. • Their science reference manual lists two common pathogens: bacteria and viruses. • Ask students how they could identify one or the other as a potential cause of the disease using the technologies available to them. • Ask a group to present its research plan. • Ask if any groups have a different research plan.	Pages 86–87 Steps 17–20
Inform the class that light microscopy did not demonstrate the presence of any structures resembling bacteria in tissue samples from affected or unaffected individuals. • On the basis of this result, students should now formulate the next step in their research plan. • Ask a group to present its research plan. • Ask whether any groups have a different research plan.	Page 87 Steps 21–23
Part 2, How Does It Work?	
Inform the class of the following results: • transmission electron microscopy demonstrated the presence of viruses in blood and muscle tissue samples from both affected and unaffected individuals; • no other tissue samples contained viruses; • there were more viruses in muscle of affected people than in unaffected people; and • the viruses appeared to be associated with actin filaments in the muscle.	Page 87 Step 1
Ask students to consider these results as they develop their plan to answer Questions 4 and 5 on the director's memo. For instance, • how do students interpret the presence of virus and the absence of disease, and • how might this relate to how the virus produces disease in susceptible individuals?	Pages 87–88 Step 2
Ask groups • to form a hypothesis based on their assessment of the data presented in Step 1, Part 2, and • to formulate a plan to test their hypothesis.	Pages 88–89 Steps 3–4

Ask a group to present its hypothesis and research plan.	Page 89 Step 5
Ask if any groups have a different hypothesis or research plan.	Page 89 Step 6
Part 3, What Can We Do About It?	
Inform the class that they must now think about developing a drug to treat the disease.	Page 89 Step 1
On the basis of the hypotheses they developed in Part 2, how might students use a drug to treat the disease?	Page 89 Step 2
Tell students that new data have been obtained. Give each group a copy of Master 3.7, *Muscle Protein Structures Determined by X-Ray Crystallography*, or use a transparency for the class.	Page 89 Step 3 **M**
Inform the class that they are to evaluate these structures and answer a series of questions, which you write on the board. • How does the structure of the affected muscle protein compare with the unaffected muscle protein? • Do these results support a way that the virus could cause the disease? • What approach might be taken to develop a drug to treat the disease? • Using the technologies available, how could potential drugs be tested for effectiveness before using them to treat humans?	Pages 89–90 Step 4
Allow groups 10 to 15 minutes to work on their responses. Reconvene the class and ask each group to present their answers.	Page 90 Step 5
Part 4, This, Too, Is What Science Is All About	
Remind students that reporting their results is also a part of doing science.	Page 91 Step 1
Instruct students to prepare a report that summarizes the work done within their group.	Page 91 Step 2

M = Involves copying a master. **T** = Involves using a transparency.

Lesson 4
Evaluate

Technology: How Much Is Enough?

At a Glance

Overview

This lesson gives students an opportunity to pull information together and demonstrate an understanding of the basic concepts discovered in earlier lessons. In the first of two activities, students use the scenario from Lesson 3 to evaluate technology from a historical perspective. They first develop timelines for key developments in biology, medicine, and technology. They then are asked, If you were a scientist in the mid-1800s, how much progress would you make in solving the problems in Lesson 3? In the second activity, students consider whether our technology toolbox is complete. They choose one of three problems and propose a technology or combination of technologies to solve it.

Major Concepts

New technologies are developed, and old technologies are improved and refined, continuously. This must be done to meet the demands created by new and existing problems.

Objectives

After completing this lesson, students will

- be able to describe the need for new or improved technologies;
- be able to explain the general process of developing technologies, including the need to have input from multiple disciplines.

Teacher Background

See the following sections in Information about Using Technology to Study Cellular and Molecular Biology:

4 Major Techniques in the Study of Cellular and Molecular Biology *(pages 26–35)*

5 Technology and the Origins of Molecular Biology *(pages 35–38)*

In Advance

Web-Based Activities

Activity	Web Version
1	No
2	No

Photocopies

Activity 1	• Master 4.1, *Microscopes Across Time*, 1 transparency • Master 4.2, *Some Key Developments in Biology, Medicine, and Technology*, 1 transparency
Activity 2	none required

Materials

Activity 1	• 24 sheets of white copying paper • black marker • blank transparency; or a string as long as the width of classroom, 29 paper clips, and 5 sheets of white copying paper
Activity 2	none required

Preparation

Activity 1
On each of 24 sheets of white paper, use the black marker to write one of the key developments listed on Master 4.2, *Some Key Developments in Biology, Medicine, and Technology* (eight developments are listed in each of three categories: biology, medicine, and technology). Do *not* provide the year of the development or the name(s) of the individual(s) involved. There are two options for this activity: use a blank transparency to record student responses as they construct the timeline for developments in biology, medicine, and technology, or stretch the string across the width of the classroom and affix it well at both ends. If you choose the second option, write *one* of the following on each of five sheets of white paper: 1600, 1700, 1800, 1900, or 2000. Use a paper clip to attach the sheet indicating 1600 at the near the left end of the string. Attach the sheet indicating 2000 near the right end of the string. Attach the remaining sheets with 1700, 1800, and 1900 in order between 1600 and 2000.

Activity 2
No preparations needed.

Activity 1: *Time Travel*

Procedure

1. **Show students the transparency of Master 4.1, *Microscopes Across Time*. Ask them to look at the pictures of the microscopes and describe the differences they observe.**

   Write student responses on the board. The pictures present microscopes developed over approximately 250 years. Students can respond to differences in design, such as the development of multiple objective lenses. Some students may respond with differences that are implied, such as better optics, electrical components, and computerized components. The objective of this question is to engage student thinking about the changing face of science and technology across time.

2. **Ask the class to imagine that they are scientists or physicians living in the mid-1800s. How much progress do they think they would make solving the problems in Lesson 3?**

   For example, could they have identified the infectious agent? Could they have determined how the disease was caused? Students will probably have little specific knowledge of when relevant discoveries were made or when relevant technologies were developed. Allow the students to wonder about the timeline of scientific discovery. Even though the problems in Lesson 3 are the same as in any time period, the technologies and knowledge available at a given time will determine the extent to which the problems can be solved.

3. **Divide the class into three groups.**

   One group will focus on biology, the second on medicine, and the third on technology.

4. **Provide each student in the biology group with one sheet on which a biology development is written. Provide each member of the medicine and technology groups with one sheet on which a development appropriate to their group is written.**

   In classes with fewer than 24 students, you can give students more than one sheet or you can give the group all eight sheets. In classes with more than 24 students, you can add the following developments:
   - biology: covalent bond described (1916, Gilbert Lewis), gene-sequencing methods developed (1977, Walter Gilbert and Allan Maxam, and Fred Sanger and Alan Coulson);

NSES

Content Standard E: Science often advances with new technologies.

- medicine: first vaccination (1796, Edward Jenner), aspirin introduced (1899, Felix Hoffmann);
- technology: protocol allowing different computer networks to interconnect and communicate with each other (1973, Vinton Cerf and Bob Kahn), automated DNA sequencer introduced (1986, Leroy Hood and colleagues).

Other developments can be added at the teacher's discretion.

5. **Ask students to estimate the year the development on their sheet occurred.**

6. **Ask students to consult with other group members to place all developments in their category in chronological order.**

   Allow only a few minutes for students to do this.

7. **Have students report their results.**

   This can be accomplished two ways. Students can call out their results to the teacher, who then records the information along a line drawn on a blank transparency projected for the class to see. Alternatively, students can clip their sheets to the string that spans the width of the room. Sheets should be placed at a location representing the approximate date of each development. For instance, a development occurring in 1850 would be placed midway between 1800 and 1900.

8. **Show students a transparency of Master 4.2, *Some Key Developments in Biology, Medicine, and Technology*, and quickly evaluate how students did at constructing their timeline.**

9. **Looking at the timeline, ask students what progress they could have made in solving the problems in Lesson 3 if they were working in the mid-1800s.**

   Students see that technologies available in 1850 were not capable of providing the information required to solve the problems in Lesson 3. Students also develop a firmer understanding of the relationship between technology development and the advancement of knowledge.

Activity 2: *Is That All There Is?*

Teacher note: This activity should follow Activity 1 without a break in discussion.

1. **Ask students if our present technology toolbox is complete. With a show of hands, how many students believe we need new technologies?**

   You might ask students to suggest some new technologies and write these suggestions on the board. Student responses are less important than shifting the focus from existing technologies to new ones (or refinements of existing ones).

2. **Tell students that they will accelerate their journey through time. They are now scientists in the year 2052. Since students know that technologies are generally developed by teams whose members have expertise in more than one discipline, they now will work in teams.**

3. **Divide the class into groups of four or five. Ask each group to choose one of the following problems:**
   - **development of a technology to detect and measure concentrations of the abnormal protein in affected people from Lesson 3 (that is, a *biosensor*),**
   - **development of a technology to determine the structure of a protein molecule without having to prepare a crystal of the protein, or**
   - **development of a technology that allows molecules of a drug to be delivered specifically to the protein of affected people from Lesson 3 in a way that allows the physician or scientist to know how much drug is delivered.**

4. **Instruct students to work with their group members to outline the requirements of their technology.**

   This is a challenging activity for students. However, the key issue is the rationale students provide for their technology. Students should consider at least the following:

   - What disciplines are involved in developing the technology?
   - Is it a new technology or a refinement of an existing technology?
   - What is the level of resolution required?
   - How are the issues of scale and probe size dealt with?
   - In general terms, how does the technology work?

5. **Reconvene the class. Each group in turn should present its technology.**

   Use class discussion to discover problems and weaknesses and to help group members refine their ideas.

Content Standard E: Many scientific investigations require contributions from different disciplines, including engineering.

Content Standard E: Creativity, imagination, and a good knowledge base are all required in the work of science and engineering.

Content Standard G: Scientific explanations must meet certain criteria such as consistency and accuracy.

6. **As a final means of assessment, ask each student to prepare a written report describing his or her technology.**

   Technologies should be described in sufficient detail to indicate the student's understanding of the concepts presented in this module.

Lesson 4 Organizer

Activity 1: *Time Travel*	
What the Teacher Does	**Procedure Reference**
Show students a transparency of Master 4.1, *Microscopes Across Time*. Ask them to look at the microscopes and describe the differences they observe.	Page 99 Step 1
Ask the class to imagine that they are scientists or physicians living in the mid-1800s. How much progress do they think they would make solving the problems in Lesson 3?	Page 99 Step 2
Divide the class into three groups. • One group will focus on biology, the second on medicine, and the third on technology. • Provide each student with a sheet of paper on which is written one development in his or her focus area. • Ask students to estimate the year the development on their sheet occurred. • Ask students to consult with other group members to place all developments in their focus area in chronological order. • Have students report their results.	Pages 99–100 Steps 3–7
Show students a transparency of Master 4.2, *Some Key Developments in Biology*. • Evaluate how students did at constructing their timeline. • Ask students what progress they could have made in solving the problems in Lesson 3 if they were working in the mid-1800s.	Page 100 Steps 8–9
Ask students, • "Is our present technology toolbox complete?" • "How many students believe we need new technologies?"	Page 101 Step 1

Divide the class into groups of four or five. • Tell students they are scientists in the year 2052. • Ask each group to choose one of the following problems: o development of a technology to detect and measure concentrations of the abnormal protein in affected people from Lesson 3; o development of a technology to determine the structure of a protein molecule without having to prepare a crystal of the protein; or o development of a technology that allows molecules of a drug to be delivered specifically to the protein of affected people from Lesson 3 in a way that allows the physician or scientist to know how much drug is delivered. • Instruct students to work with their group members to outline the requirements of their technology, focusing on concepts learned in earlier lessons.	Page 101 Steps 2–4
Reconvene the class and allow each group to present its technology.	Page 101 Step 5
As a final assessment, ask each student to prepare a written report describing his or her technology.	Page 102 Step 6

T = Involves using a transparency.

Masters

Lesson 1, *What Is Technology?*

Master 1.1, *Searching for Scale* ..... 1 copy per student

Lesson 2, *Resolving Issues*

Master 2.1, *Probing for Answers Score Sheet* ..... 1 copy per 2 students, 1 transparency

Master 2.2, *Probes* ..... 1 copy per 12 students

Masters 2.3 to 2.8, *Probing for Answers—Levels 1–6* ..... 1 copy of each per 12 or fewer students; 2 copies of each for 13–24 students; 3 copies of each for 25–36 students

Master 2.9, *Solution to Probing for Answers* ..... 1 transparency (*print version* only)

Lesson 3, *Putting Technology to Work*

Master 3.1, *Memo from the Director, Global Science and Health Organization* ..... 1 copy per group

Master 3.2, *Research Plan* ..... 1 copy per student, 1 transparency

Master 3.3, *Example of a Research Plan* ..... 1 transparency

Master 3.4, *Drug Discovery Evaluation Form* ..... 1 copy per student (*Web version* only)

Master 3.5, *Available Technologies* ..... 1 transparency (*print version* only)

Master 3.6, *Science Reference Manual* ..... 1 copy per group (*print version* only)

Master 3.7, *Muscle Protein Structures Determined by X-Ray Crystallography* ..... 1 copy per group or 1 transparency (*print version* only)

Lesson 4, *Technology: How Much Is Enough?*

Master 4.1, *Microscopes Across Time* ..... 1 transparency

Master 4.2, *Some Key Developments in Biology, Medicine, and Technology* ..... 1 transparency

Searching for Scale

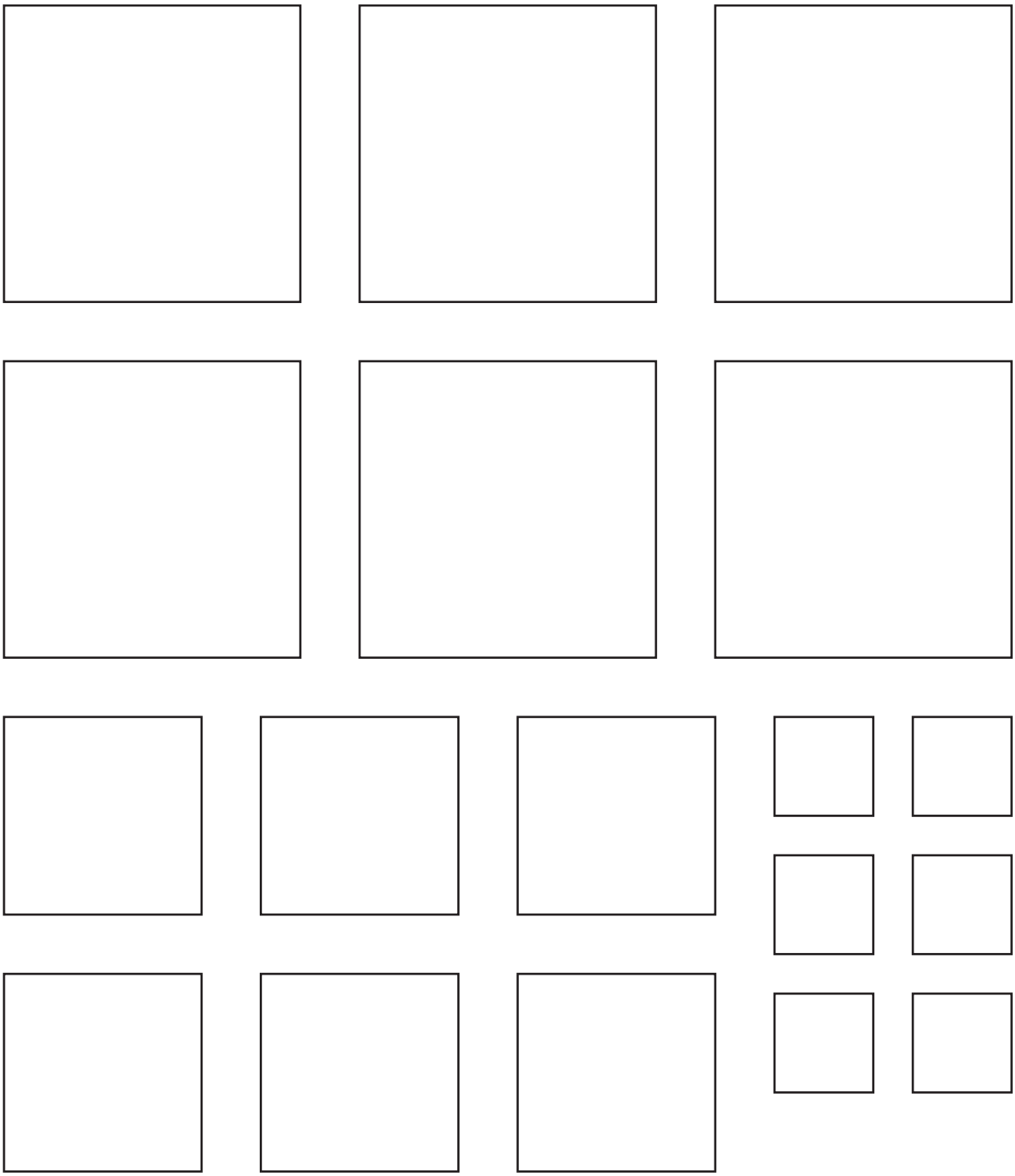
Name: _____ Date: _____

Biological Structure	Actual Diameter (in Meters)	Size Relative to Cell	Object Used to Model Biological structure	Measured Size of Model Object	Size Relative to Model Cell (the Room)
Cell	1×10^{-5}	$\frac{1 \times 10^{-5}}{1 \times 10^{-5}} = 1$	Room	10 meters	$\frac{10}{10} = 1$
Bacterium	1×10^{-6}	$\frac{1 \times 10^{-6}}{1 \times 10^{-5}} = \frac{1}{10}$	Desk	1 meter	$\frac{1}{10} = \frac{1}{10}$
Mitochondrion	5×10^{-7}	$\frac{5 \times 10^{-7}}{1 \times 10^{-5}} = \frac{1}{20}$			
Virus	1×10^{-7}				
Ribosome	1×10^{-8}				
Protein	5×10^{-9}				
Glucose molecule	1×10^{-9}				
H_2O molecule	1×10^{-10}				

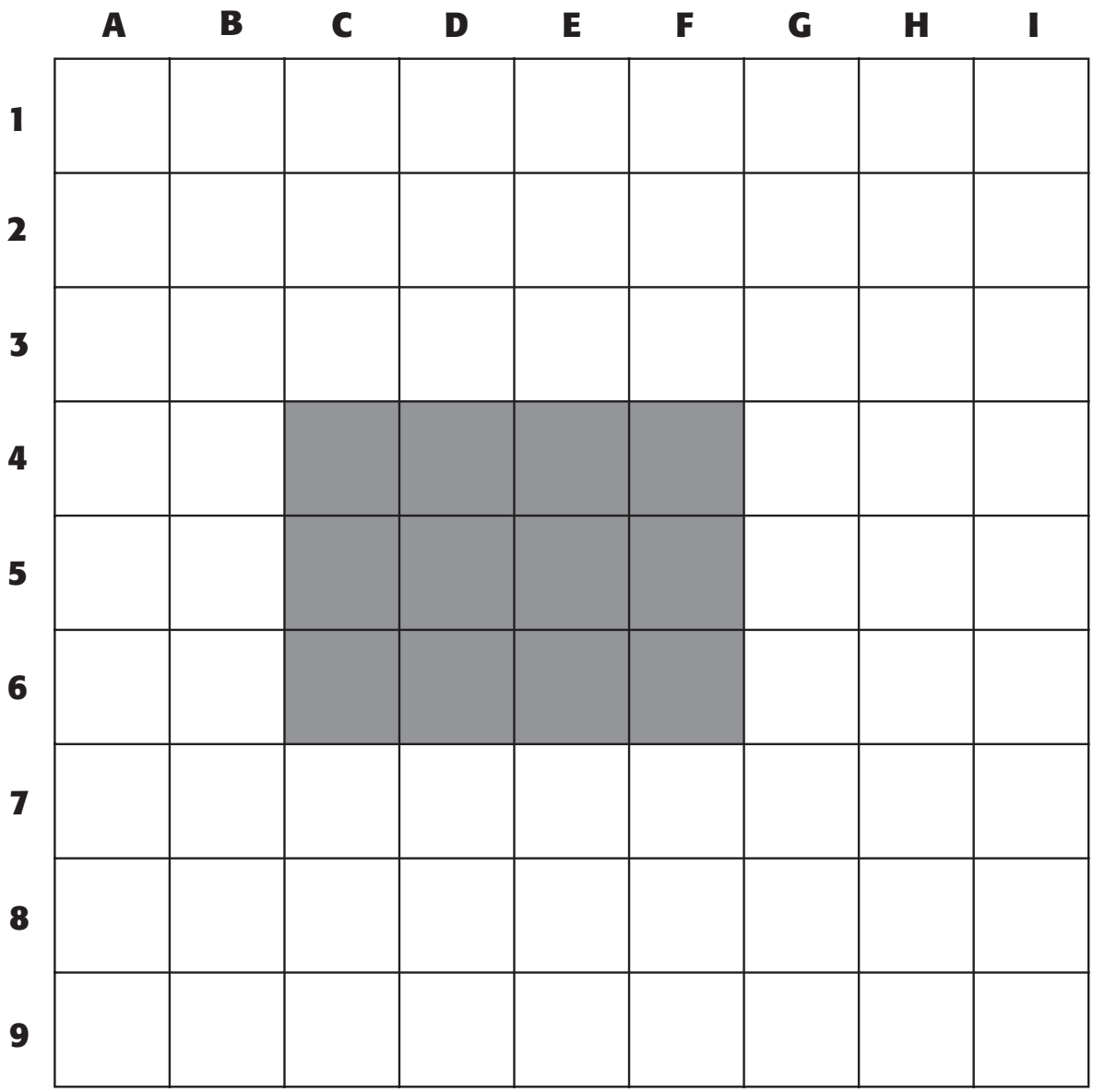
Probing for Answers Score Sheet

	A	B	C	D	E	F	G	H	I
1									
2									
3									
4									
5									
6									
7									
8									
9									

Probes

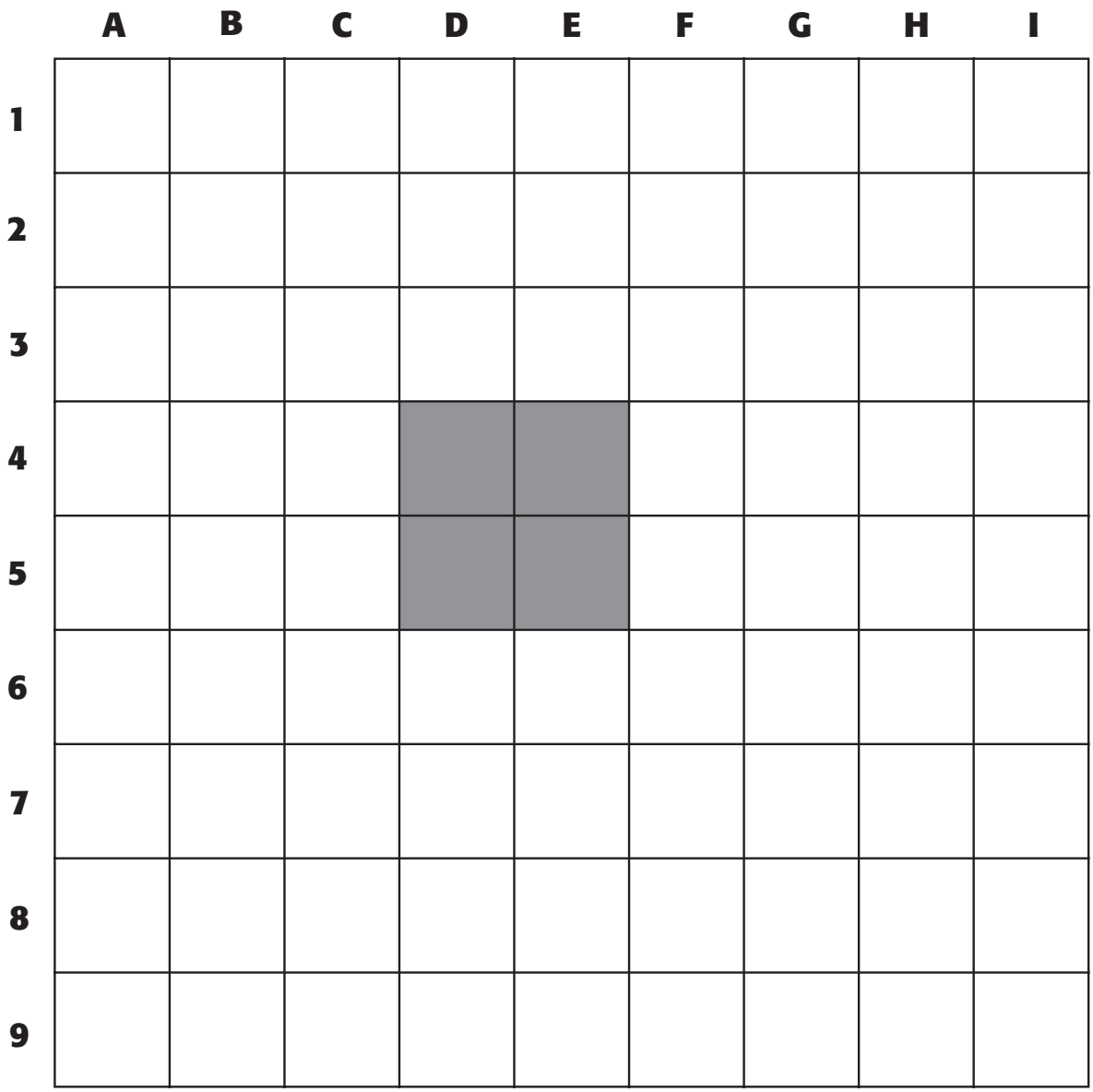


Probing for Answers—Level 1



Level 1

Probing for Answers—Level 2



Level 2

Probing for Answers—Level 3

	A	B	C	D	E	F	G	H	I
1									
2									
3									
4									
5									
6									
7									
8									
9									

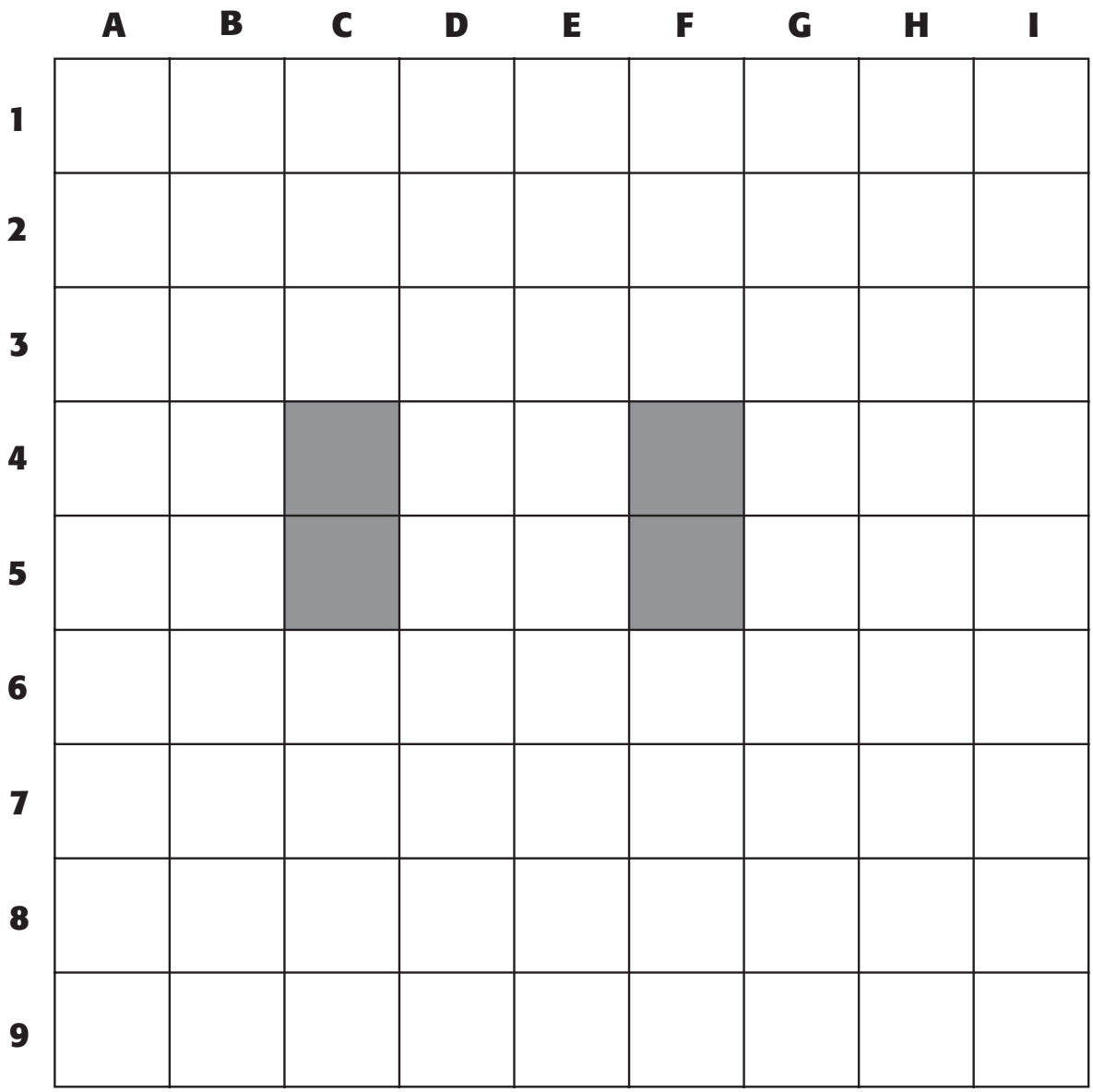
Level 3

Probing for Answers—Level 4

	A	B	C	D	E	F	G	H	I
1									
2									
3									
4									
5									
6									
7									
8									
9									

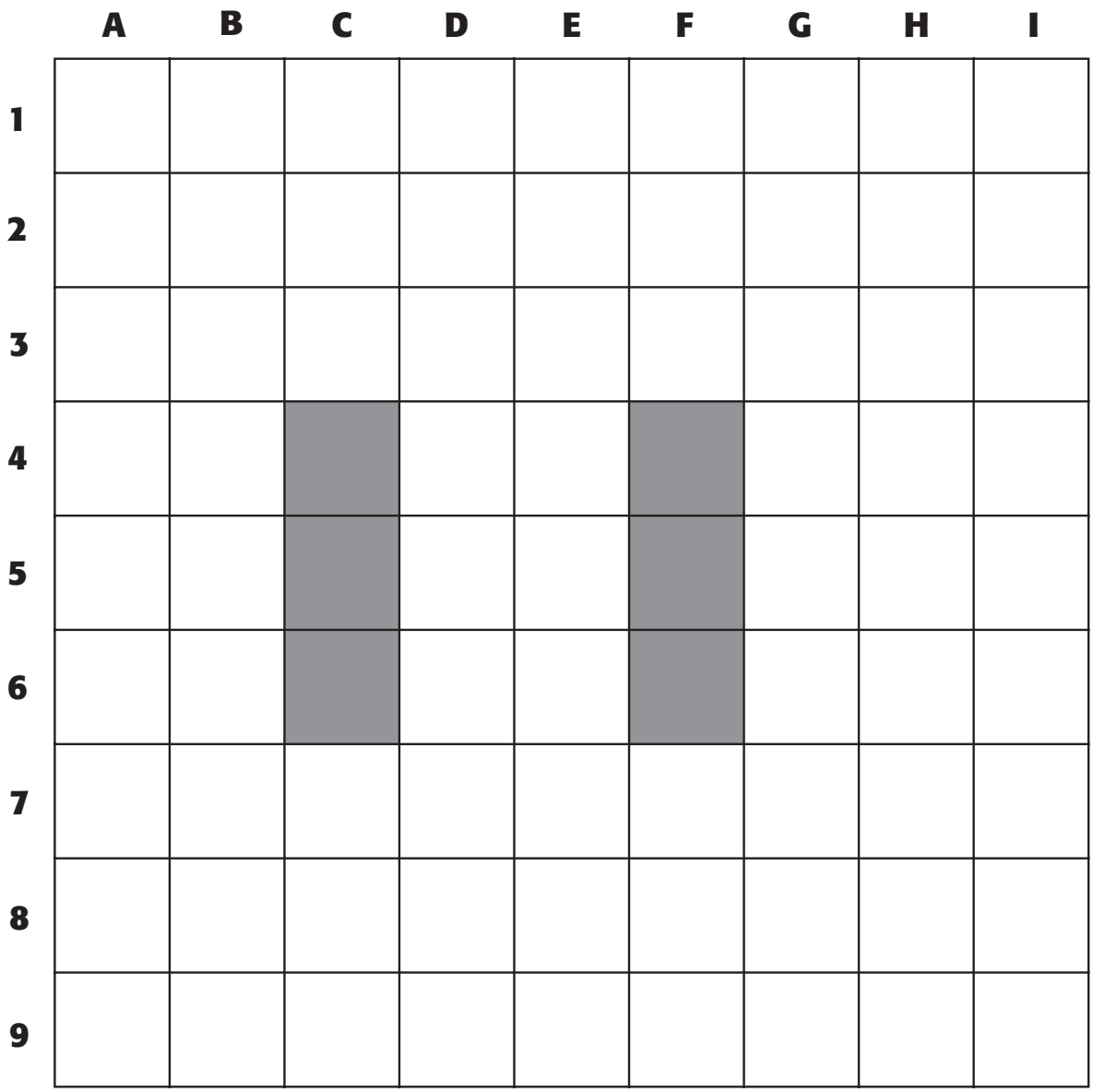
Level 4

Probing for Answers—Level 5



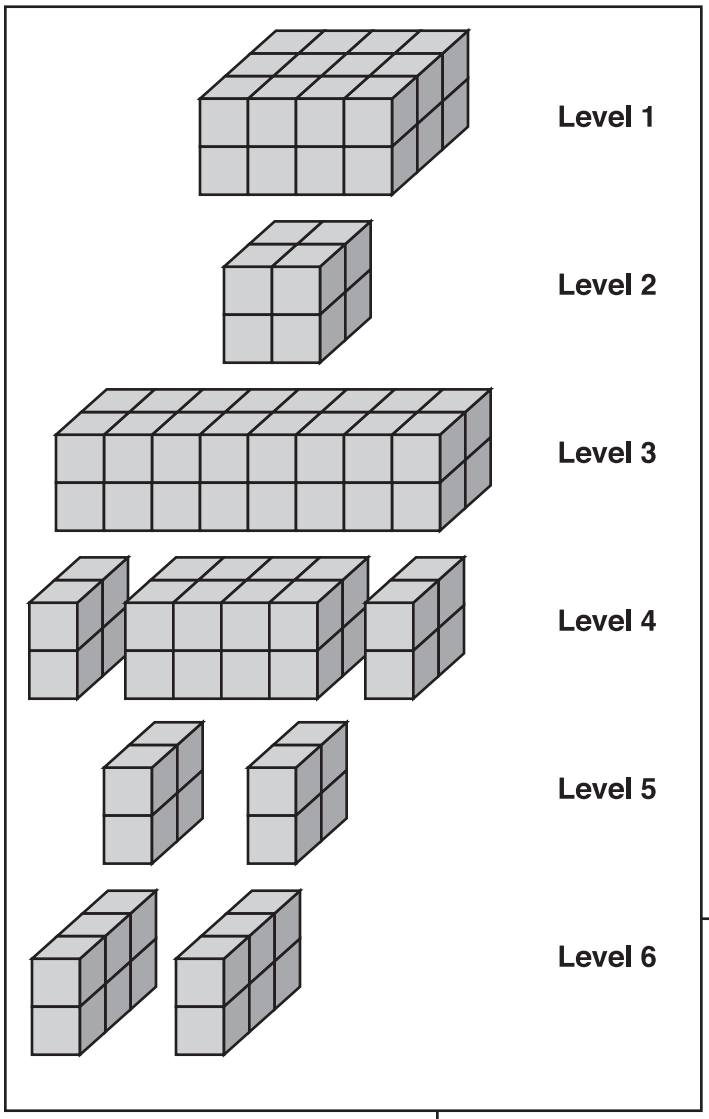
Level 5

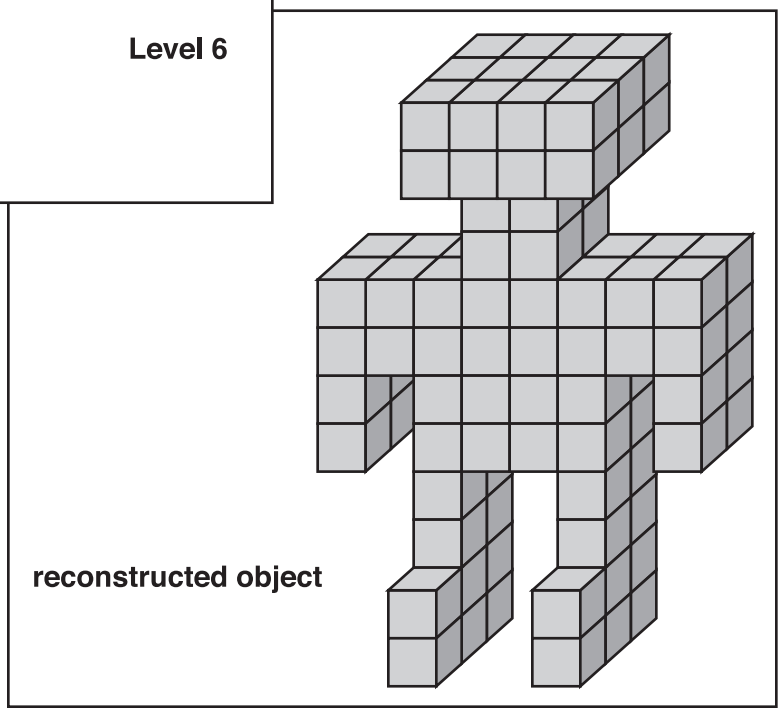
Probing for Answers—Level 6



Level 6

Solution to Probing for Answers





Memo from the Director, Global Science and Health Organization

Global Science and Health Organization

Memo

TO: Members, Scientific and Health Evaluation Teams

FROM: Director, Global Science and Health Organization

RE: New disease

Our Division of Disease Surveillance recently reported a new disease affecting approximately 30% of the persons living in a small rural area of the United States. Affected individuals have a lack of energy and demonstrate a progressive loss of muscle function. Although we have no information yet, we believe the disease is caused by an infectious agent. Consequently, to limit the spread of this disease, immediate intervention is critical.

We need your expertise to answer these questions:

1. Is there evidence of disease at the cellular level? If so,
2. Is the disease caused by an infectious agent? If it is,
3. What is the infectious agent?
4. Does the infectious agent attack muscle tissue?
5. How might the infectious agent cause the disease?
6. Is there a drug to treat or prevent the disease?

Blood and muscle tissue samples from unaffected and affected individuals are waiting for you. The microscopy and X-ray crystallography facilities at GSHO are being readied for your arrival. In order to gain information as quickly as possible, please develop a solid research plan before beginning your investigations.

Good luck!

Research Plan

Name: _____ Date: _____

1. To answer the question, _____

_____

2. I will use this technology: _____

_____

3. I chose this technology because _____

_____

4. My hypothesis is _____

_____

5. I expect one of the following two results: _____

_____

6. Observations (actual results) and interpretation:

Example of a Research Plan

1. To answer the question, Is there evidence of disease at the cellular level (in muscle cells)?

2. I will use this technology: Light Microscope

3. I chose this technology because its resolution level allows me to see muscle cells.

4. My hypothesis is There is evidence of disease in muscle cells.

5. I expect one of the following two results: I will see abnormal muscle cells in affected individuals OR I will see NO abnormal muscle cells in affected individuals.

6. Observations (actual results) and interpretation:

Result 1—Muscle cells from affected individuals are different from normal muscle cells and those from unaffected individuals; interpreted as evidence of disease in muscle of affected individuals. Proceed to next question.

1. To answer the question, Is the disease caused by an infectious agent (bacteria)?

2. I will use this technology: Light Microscope

3. I chose this technology because its resolution level allows me to see bacteria.

4. My hypothesis is (continue as above).

OR

6. Observations (actual results) and interpretation:

Result 2—Muscle cells from affected individuals appear the same as normal muscle cells and muscle cells from unaffected individuals. Interpreted as lack of evidence of disease in muscle cells of affected individuals. Look for evidence of disease in other tissues.

1. To answer the question, Is there evidence of disease at the cellular level (blood)?

2. I will use this technology: Light Microscope

3. I chose this technology because its resolution level allows me to see blood cells.

4. My hypothesis is (continue as above).

Drug Discovery Evaluation Form

Name: _____ Date: _____

Molecule 1: Evaluation of X-ray crystallography, protein structure data:

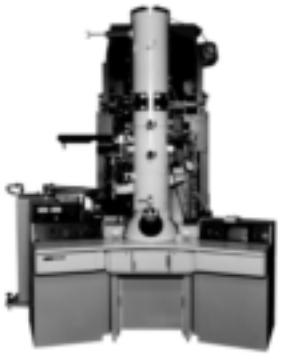
Molecule 2: Evaluation of X-ray crystallography, protein structure data:

Molecule 3: Evaluation of X-ray crystallography, protein structure data:

Molecule 4: Evaluation of X-ray crystallography, protein structure data:

Overall evaluation: Is there a drug you would recommend to treat the disease? Justify your response.

Available Technologies

				
	eye	Light Microscopes	Electron Microscopes	X-Ray Techniques
Probe	Visible Light	Visible Light	Electrons	X-rays
Approximate Resolution	10^{-4} m	10^{-7} m	10^{-10} m	10^{-11} m

Master 3.5

Science Reference Manual

Science Reference Manual

Table of Contents

Section 1: Technology
- Light Microscopy
- Electron Microscopy
- X-Ray Crystallography

Section 2: Infectious Disease Causative Agents
- Infectious Disease
- Bacteria
- Viruses

Section 3: Blood

Section 4: Muscle
- Muscle Structure
- Muscle Proteins
- Muscle Contraction

Section 5: Drug Discovery
- Rational Basis for New Drug Development

Light Microscopy

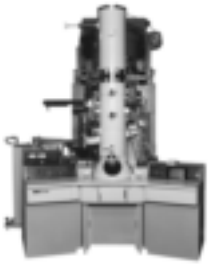
The first microscopes were optical ones, which use glass lenses to focus and magnify light. Although Hans and Sacharias Janssen constructed the first optical microscope in 1595, it was not until 60 to 80 years later that major discoveries were made with this technology. In the late 1600s, Antonio van Leeuwenhoek improved the lenses used in microscopes, allowing magnification to be increased from 50x to 200x. There were additonal improvements to optical microscopy over the next 300 years, which ultimately increased magification up to 1,500x and allowed optical microscopes to resolve objects as small as 200 nanometers (nm; 2×10^{-7} m). This resolution is a physical limit dictated by the wavelength of light (that is, its size as a probe).

Electron Microscopy

The first electron microscope (EM) was built in 1933 by Ernst Ruska (1986 Nobel Prize winner for achievements in electron optics). Ruska used accelerated electrons and magnetic coils to make an image instead of light and glass lenses. Electrons have a wavelength (size) that is 10^4 to 10^5 times smaller than the wavelength of light. EMs can resolve objects that are 10^3 times smaller than the smallest resolvable object in a light microscope.

Transmission EMs yield information similar to transmission light microscopes about the size, shape, and arrangement of particles in a specimen, although at much higher resolution. The high-resolution transmission EM can magnify a sample up to 50,000x and provide a resolution of 0.1 nm (0.1×10^{-9} m).

Transmission EM



High-Resolution Transmission EM

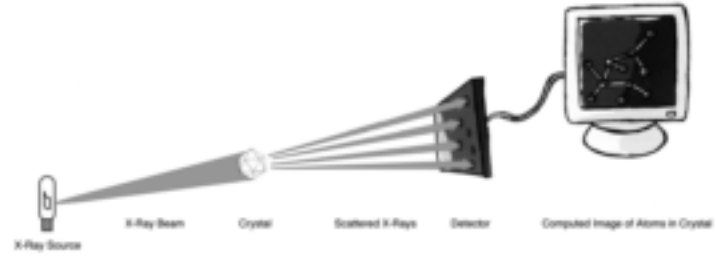
The resolution of EMs can be improved through modifications of the sample preparation procedure. In cryo-EM, specimens are frozen rapidly to eliminate ice crystals from forming that can distort the specimen's structure. Samples are then viewed at temperatures as low as –185°C.

Two- and three-dimensional models of the sample can be reconstructed using a computer program that averages many electron micrographs taken from different angles.

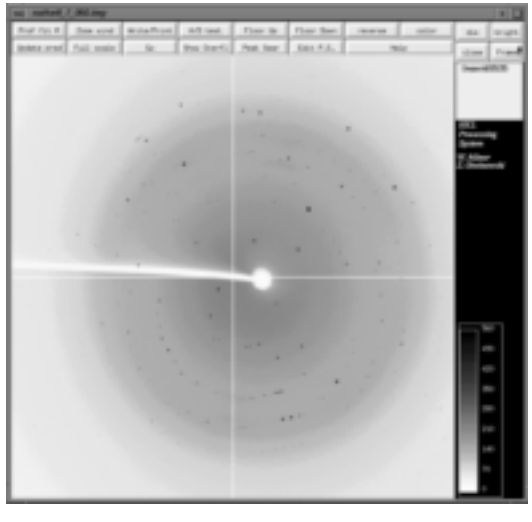
Cryo-EM

Electron microscopy requires a sample thin enough to allow electrons to pass through. Samples smaller than 1/500th the diameter of a human hair are used. In a transmission EM, electrons pass through the sample and are imaged on a fluorescent screen at the bottom of the microscope column. Samples that are more electron dense allow fewer electrons to pass through. This results in a darker image. In some cases, chemicals that are electron dense and bind to specific cellular components are used as stains. These stains make it possible to view cell components that themselves are not electron dense.

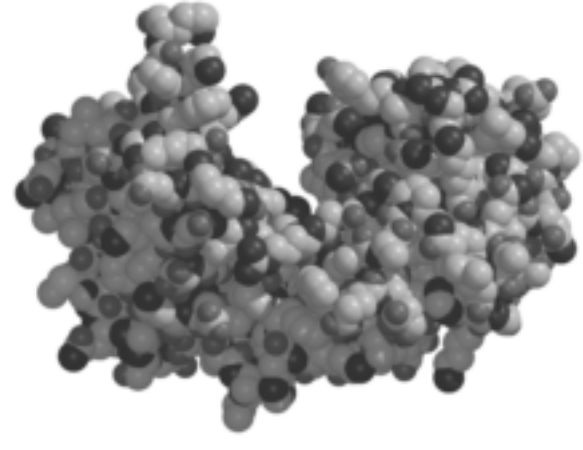
X-Ray Crystallography



X-rays, with wavelengths approximately the same size as the spacing between atoms, are directed through a crystal of the substance under study. The X-rays are bent by the electrons surrounding the atoms in the crystal. The scattered X-rays produce a pattern as they exit the crystal. Locations at which X-rays are received by a detector are recorded as dark spots on a film. Sophisticated computer programs use measurements of the angles of the scattered X-rays and their intensities to calculate the three-dimensional positions of the atoms in the crystal. By rotating the crystal and making many two-dimensional images, it is possible to combine results to produce a three-dimensional picture of the molecule.



This is a typical diffraction pattern produced by passing X-rays through a protein crystal. The dark spots represent intensities of X-rays and places where X-rays have struck the detector. Scientists measure the location and intensity of the scattered X-rays. The white circle to the right of center with the white line extending to the left is a shadow from a "beamstop." The beamstop is a small piece of lead mounted on a metal arm. It protects the detector from the intense beam of unscattered X-rays.



Sophisticated computer programs convert the data from X-ray crystallography patterns into three-dimensional models of proteins, such as the one above of MutY, a DNA-repair protein.

Science Reference Manual

Infectious Disease

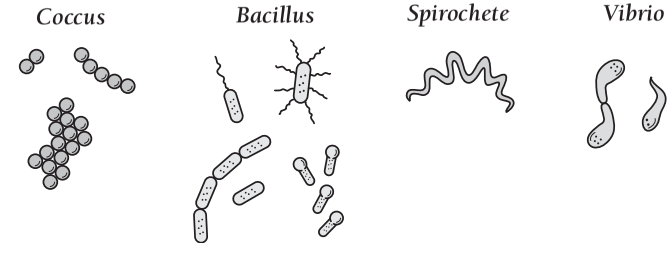
Infectious diseases result when an organism or other agent enters the body and reproduces itself. Infectious agents, or *pathogens*, can produce disease in several ways. For instance, pathogens can produce chemical agents, such as proteins or other small molecules, which can damage tissue. Also, the chemical agents can interfere with normal cellular processes or act as toxins.

The most common pathogens are bacteria and viruses. Other pathogens include fungi, worms, and protozoans.

Bacteria

Bacteria are single-celled prokaryotic organisms. Most bacteria are from 0.3 to 2.0×10^{-6} m in diameter. Most are harmless, and many perform helpful functions. Only a small number of bacteria are pathogens. Cholera, leprosy, pneumonia, tuberculosis, and whooping cough are examples of human diseases caused by bacteria that destroy healthy cells. Diphtheria, scarlet fever, tetanus, and botulism are human diseases caused by toxins that bacteria produce.

Bacteria are divided into groups according to shape, as seen below. Some bacteria may be found in small groups or clusters.



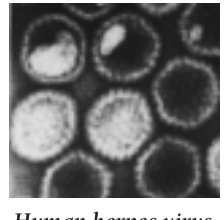
Viruses

Viruses are small particles consisting of a core of nucleic acid and an outer coat of protein. They live within cells of living organisms. Viruses generally are rods or spheres that range in size from about 0.1 to 3×10^{-7} m. The word *virus* is derived from a Latin word meaning *poison*. This is appropriate since viruses are a major cause of disease, even though some viruses are harmless. Diseases in humans that viruses cause include AIDS, chickenpox, colds, influenza, cold sores, measles. mumps, and rabies.

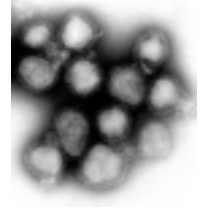
The protein coat of a virus gives the particle its characteristic shape, as illustrated in the following examples:

Ebola virus from EM

Rabies virus from EM

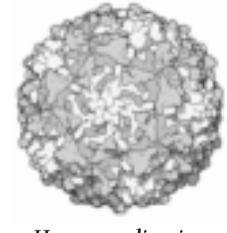


Human herpes virus from EM



Human influenza virus from EM

Human papilloma virus from EM

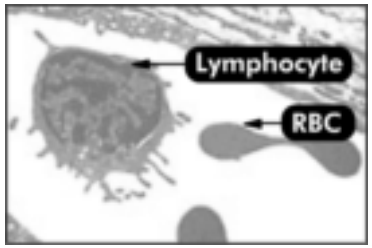


Human polio virus from cryo-EM reconstruction

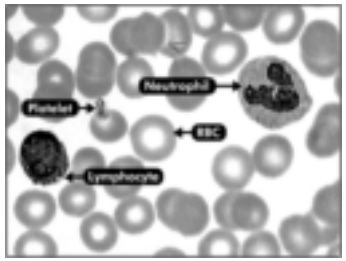
Viruses attach to proteins called *receptors* on the surface of cells. This allows the virus or its nucleic acid to enter the cell. Proteins encoded by the virus's nucleic acid can then be produced by the cell. These proteins may affect cell functions by binding to cell proteins, altering metabolism, or some other means. They also may be used to manufacture new virus particles.

Science Reference Manual

Blood



Transmission EM of lymphocyte and red blood cell (RBC) (2,000x).



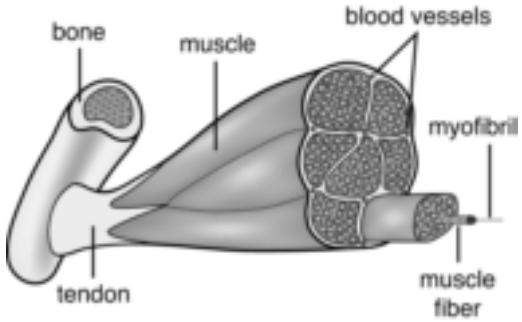
Blood smear viewed at 400x with a light microscope.

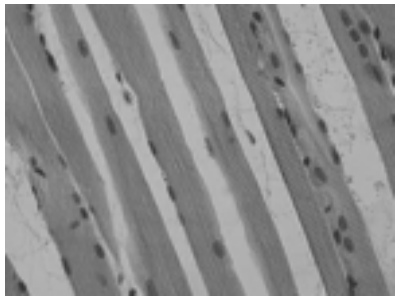
Approximately 55 percent of blood is a straw-colored clear liquid called plasma. The remainder of blood is composed of various cell types, as seen above.

Red blood cells are disc-shaped and contain hemoglobin, a protein to which oxygen binds. Neutrophils and lymphocytes are the major white blood cells. These provide the body's major defense against infection. Platelets are small cells involved in blood clotting.

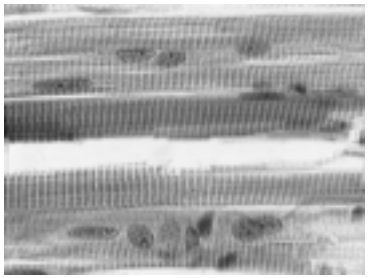
Muscle Structure

Skeletal muscle, also known as striated muscle, is made of many muscle fibers, each of which extends the length of the muscle (up to 2.5 feet long). Muscle fibers are arranged parallel to one another, and a membrane called the sarcolemma bundles them together. Each fiber contains multiple nuclei and numerous mitochondria, because each muscle fiber develops from the fusion of many cells called myofibrils that extend the length of the fiber.

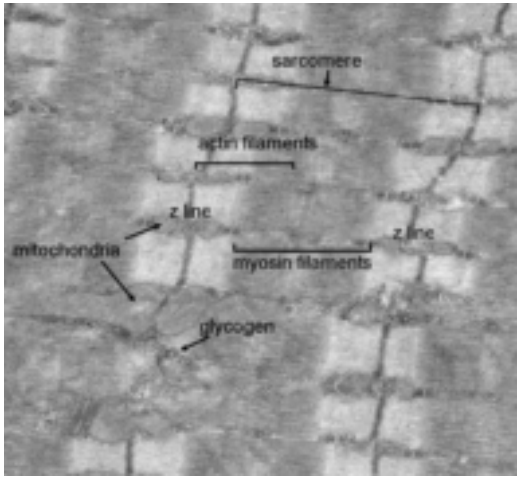




Light micrograph of a longitudinal section of normal skeletal muscle; dark oval structures are nuclei.



Light micrograph showing striated appearance of normal muscle fiber.



Electron micrograph of human skeletal muscle.

Each myofibril is made of two kinds of parallel filaments. *Thick filaments* are 1.6×10^{-6} m long and made of myosin. *Thin filaments* are 1×10^{-6} m long and made of actin. Thin filaments extend in both directions from a protein that forms a region called the z line.

The area between two z lines is a sarcomere. This is the functional unit of skeletal muscle. Sarcomeres are the smallest units that can perform all of the functions of muscle tissue.

Science Reference Manual

Muscle Proteins

Muscle fibers are made up of many different proteins arranged in a specific way. Their arrangement and individual properties allow muscle to function. Some proteins serve structural roles, while others are directly involved in muscle contraction and relaxation.

Up to one-fifth of the protein in muscle cells is actin, which forms the thin filaments of the cells.

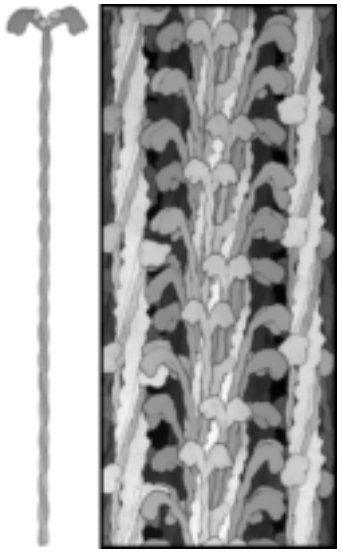
About 360 actin molecules combine to form a long chain. Two of these chains are twisted into a double helix to form an actin filament. Specialized proteins stabilize the filament.

Cryo-EM reconstruction of an actin double helix.

Myosin makes up about 45 to 50 percent of muscle contractile proteins and is the major protein of the think filaments.

Myosin uses chemical energy to perform motion. The myosin molecule looks somewhat like two golf clubs with their shafts wrapped around each other.

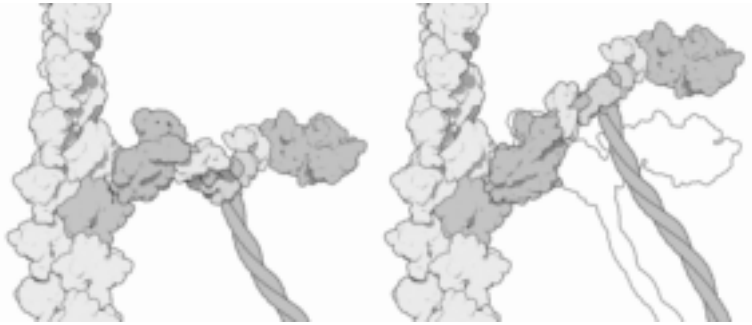
Several other proteins help maintain the structure of the thick filaments.



Cryo-EM reconstruction of a myosin molecule (left) and a thick myosin filament in between two thin actin filaments (right).

Muscle Contraction

At the tip of the myosin molecule is a cleft that binds to the actin filament. The lever arm of the myosin pushes the myosin molecule along the actin filament. Muscle contraction requires actin, myosin, and other proteins, the important mineral calcium, and energy in the form of adenosine triphosphate (ATP).



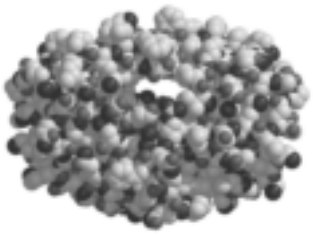
Rational Basis for New Drug Development

The key to rational drug design is understanding the structure and function of biological molecules involved in disease development. To develop drugs that fight disease, scientists search for chemical and biological substances that target cellular and molecular factors that play a role in disease. Many tools are used in rational drug design, including microscopic techniques, X-ray techniques, computer analyses, and simulations.

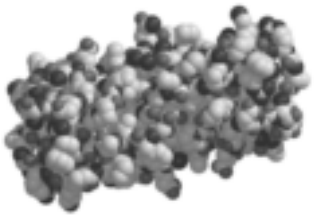
The aim of rational drug design is to produce drugs with greater selectivity and, therefore, greater effectiveness. The approach differs from the traditional medicinal approach, which relies on more extensive and random testing.

Muscle Protein Structures Determined by X-Ray Crystallography

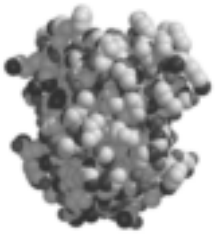
Muscle protein from affected people



Along z-axis

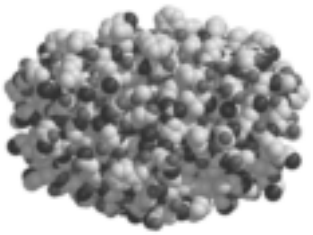


Along x-axis

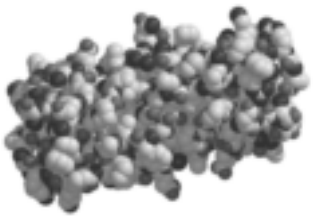


Along y-axis

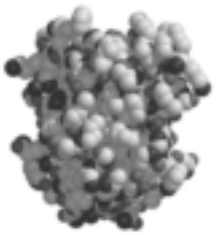
Muscle protein from unaffected people



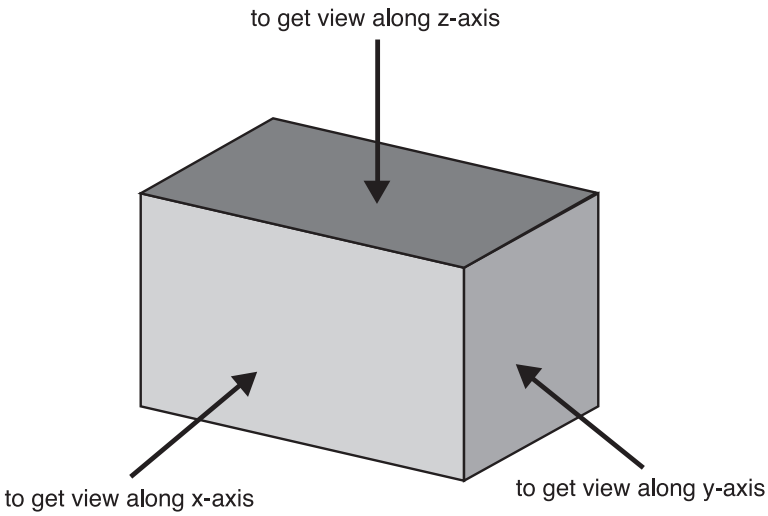
Along z-axis



Along x-axis



Along y-axis



Master 3.7

Microscopes Across Time

1754
Culpepper microscope

1850
Ross microscope

1909
Leitz Wetzler microscope

1948
Spencer microscope

2004
Modern research microscope

Some Key Developments in Biology, Medicine, and Technology, by Year

BIOLOGY

1665	Cells first described (Robert Hooke).
1839	Proposal made that animal tissues are composed of cells (Theodor Schwann).
1869	DNA discovered (Friedrich Miescher).
1911	Structure of the atom discovered (Ernest Rutherford).
1942	Myosin *and* actin reported to be the main structural proteins of muscle (Albert Szent-Gyorgi and colleagues).
1953	Double helix model of DNA proposed (James Watson and Francis Crick; their model was supported by X-ray crystallography done by Maurice Wilkins and Rosalind Franklin).
1953	Structure of hemoglobin determined using X-ray crystallography (Max Perutz and John Kendrew).
2000	Atomic structure of the large subunit of a bacterial ribosome resolved using X-ray crystallography (Thomas Steitz and colleagues).

MEDICINE

1862	Germ theory published: infection is caused by bacteria (Louis Pasteur).
1868	First diagnosis made of a complex disease, multiple sclerosis (Jean Martin Charcot).
1892	Viruses discovered (Dimitri Ivanovsky).
1892	White blood cells identified (Elie Metchnikoff).
1893	First modern American medical school opens (Johns Hopkins University, Baltimore, Md.).
1895	First pharmaceutical research laboratory founded (Parke-Davis Company, Detroit, Mich.).
1928	Penicillin discovered (Alexander Fleming).
1959	First major drug to treat leukemia invented (Gertrude Elion).

TECHNOLOGY

1593	Thermometer invented (Galileo).
1883	First induction motor constructed, the basis of generating electricity (Nicola Tesla).
1895	X-rays discovered (Wilhelm Conrad Roentgen).
1912	X-ray crystallography invented (William Bragg).
1923	First electric refrigerator produced (Electrolux, Old Greenwich, Conn.).
1927	First working model of television (Philo Farnsworth).
1932	Electron microscope invented (Max Knoll and Ernst Ruska).
1969	First microprocessor designed, the basis for computer development (Marcian Hoff).