

Preface to the First Edition

This book is in essence the lectures I give in my plant cell biology course at Cornell University. Heretofore, the lecture notes have gone by various titles, including "Cell La Vie," "The Book Formerly Known as Cell La Vie," "Molecular Theology of the Cell," "Know Thy Cell" (with apologies to Socrates), "Cell This Book" (with apologies to Abbie Hoffman), and "Impressionistic Plant Cell Biology." I would like to take this opportunity to describe this course. It is a semester-long course for undergraduate and graduate students. Because the undergraduate biology majors are required to take genetics, biochemistry, and evolution as well as 1 year each of mathematics and physics and 2 years of chemistry, I have done my best to integrate these disciplines into my teaching. Moreover, many of the students also take plant anatomy, plant physiology, plant growth and development, plant taxonomy, plant biochemistry, plant molecular biology, and a variety of courses that end with the suffix "-omics"; I have tried to show the connections between these courses and plant cell biology. Nonbotanists can find a good introduction to plant biology in Mauseth (2009) and Taiz and Zeiger (2006).

Much of the content has grown over the past 20 years from the questions and insights of the students and teaching assistants who have participated in the class. The students' interest has been sparked by the imaginative and insightful studies done by the worldwide community of cell biologists, which I had the honor of presenting.

I have taken the approach that real divisions not only exist between subject areas taught in a university but only in the state of mind of the teachers and researchers. With this approach, I hope that my students do not see plant cell biology as an isolated subject area, but as an entry into every aspect of human endeavor. One of the goals of my course is to try to reestablish the connections that once existed between mathematics, astronomy, physics, chemistry, geology, philosophy, and biology. It is my own personal attempt, and it is an ongoing process. Consequently, it is far from complete. Even so, I try to provide the motivation and resources for my students to weave together the threads of these disciplines to create their own personal tapestry of the cell from the various lines of research.

Recognizing the basic similarities between all living eukaryotic cells (Quekett, 1852, 1854; Huxley, 1893), I discuss both animal and plant cells in my course. Although the examples are biased toward plants (as they should be in a plant cell biology course), I try to present the best example to illustrate a process and sometimes the best examples are from animal cells. I take the approach used by August Krogh (1929), that is, there are many organisms in the treasure house of nature and if one respects this treasure, one can find an organism created to best illuminate each principle! I try to present my course in a balanced manner, covering all aspects of plant cell biology without emphasizing any one plant, organelle, molecule, or technique. I realize, however, that the majority of papers in plant cell biology today are using a few model organisms and "-omic" techniques. My students can learn about the successes gained through this approach in a multitude of other courses. I teach them that there are other approaches.

Pythagoras believed in the power of numbers, and I believe that the power of numbers is useful for understanding the nature of the cell. In my class, I apply the power of numbers to help relate quantities that one wishes to know to things that can be easily measured (Hobson, 1923; Whitehead, 1925; Hardy, 1940; Sygne, 1951, 1970; Feynman, 1965a; Schrödinger, 1996). For example, the area of a rectangle is difficult to measure. However, if one knows its length and width, and the relation that area is the product of length and width, the area can be calculated from the easily measurable quantities. Likewise, the circumference or area of a circle is relatively difficult to measure. However, if one measures the diameter and multiplies it by π , or the square of the diameter by $\pi/4$, one can easily obtain the circumference and area, respectively. In the same way, one can easily estimate the height of a tree from easily measurable quantities if one understands trigonometry and the definition of tangent.

My teaching was greatly influenced by a story that Hans Bethe told at a meeting at Cornell University commemorating the 50th anniversary of the chain reaction produced by Enrico Fermi. Bethe spoke about the difference between his graduate adviser, Arnold Sommerfeld, and his postdoctoral adviser, Enrico Fermi. He said that, in the field of atomic

physics, Sommerfeld was a genius at creating a mathematical theory to describe the available data. Sommerfeld's skill, however, depended on the presence of data. Fermi, on the other hand, could come up with theories even if the relevant data were not apparent. He would make estimates of the data from first principles. For example, he estimated the force of the first atomic bomb by measuring the distance small pieces of paper flew as they fell to the ground during the blast in Alamogordo. Knowing that the force of the blast diminished with the square of the distance from the bomb, Fermi estimated the force of the bomb relative to the force of gravity. Within seconds of the blast, he calculated the force of the bomb to be approximately 20 kilotons, similar to which the expensive machines recorded (Fermi, 1954; Lamont, 1965).

To train his students to estimate things that they did not know, Fermi would ask them, "How many piano tuners are there in Los Angeles?" After they looked befuddled, he would say, "You can estimate the number of piano tuners from first principles! For example, how many people are there in Los Angeles? One million? What percentage has pianos? Five percent? Then there are 50,000 pianos in Los Angeles. How often does a piano need to be tuned? About once a year? Then 50,000 pianos need to be tuned in a year. How many pianos can a piano tuner tune in a day? Three? Then one tuner must spend 16,667 days a year tuning pianos. But since there are not that many days in a year, and he or she probably only works 250 days a year, then there must be around 67 piano tuners in Los Angeles."

My students apply the power of numbers to the study of cellular processes, including membrane transport, photosynthesis, and respiration, to get a feel for these processes and the interconversions that occur during these processes between different forms of energy. My students apply the power of numbers to the study of cell growth, chromosome motion, and membrane trafficking to postulate and evaluate the potential mechanisms involved in these processes, and the relationships between these processes and the bioenergetic events that power them. Becoming facile with numbers allows the students to understand, develop, and critique theories. "As the Greek origin of the word [theory] implies, the Theory is the true seeing of things—the insight that should come with healthy sight" (Adams and Whicher, 1949).

Using the power of numbers to relate seemingly unrelated processes, my students are able to try to analyze all their conclusions in terms of first principles. They also learn to make predictions based on first principles. The students must be explicit in terms of what they are considering to be facts, what they are considering to be the relationship between facts, and where they are making assumptions. This provides a good entry into research because the facts must be refined and the assumptions must be tested (East, 1923).

I do not try to introduce any more terminology in my class than is necessary, and I try to explain the origin of each term. Some specialized terms are essential for precise communication in science just as it is in describing love and beauty. However, some terms are created to hide our ignorance, and consequently prevent further inquiry, because something with an official-sounding name seems well understood (Locke, 1824; Hayakawa, 1941; Rapoport, 1975). In Goethe's (1808) "Faust Part One," Mephistopheles says: "For at the point where concepts fail. At the right time a word is thrust in there. With words we fitly can our foes assail." Francis Bacon (1620) referred to this problem as the "Idols of the Marketplace." Often we think we are great thinkers when we answer a question with a Greek or Latin word. For example, if I am asked, "Why are leaves green?" I quickly retort, "Because they have chlorophyll." The questioner is satisfied, and says "Oh." The conversation ends. However, chlorophyll is just the Greek word for green leaf. Thus, I really answered the question with a tautology. I really said "Leaves are green because leaves are green" and did not answer the question at all. It was as if I was reciting a sentence from scripture, which I had committed to memory without giving it much thought. However, I gave the answer in Greek, and with authority ... so it was a scientific answer.

In "An Essay Concerning Human Understanding," John Locke (1824) admonished that words are often used in a nonintellectual manner. He wrote,

... he would not be much better than the Indian before-mentioned, who, saying that the world was supported by a great elephant, was asked what the elephant rested on; to which his answer was, a great tortoise. But being again pressed to know what gave support to the broad-backed tortoise, replied, something he knew not what. And thus here, as in all other cases where we use words without having clear and distinct ideas, we talk like children; who being questioned what such a thing is, which they know not, readily give the satisfactory answer, that it is something; which in truth signifies no more, when so used either by children or men, but that they know not what; and that the thing that they pretend to know and talk of is what they have no distinct idea of at all, and so are perfectly ignorant of it, and in the dark.

Sometimes terms are created to become the shibboleths of a field, and sometimes they are created for political reasons, financial reasons, or to transfer credit from someone who discovers something to someone who renames it

(Agre et al., 1995). Joseph Fruton (1992) recounted (and translated) a story of a conversation with a famous chemist in Honoré de Balzac's *La Peau de Chagrin*:

"Well, my old friend," said Planchette upon seeing Japhet seated in an armchair and examining a precipitate, "How goes it in chemistry?"

It is asleep. Nothing new. The Académie has in the meantime recognized the existence of salicine. But salicine, asparagine, vauqueline, digitaline are not new discoveries.

"If one is unable to produce new things," said Raphael, "it seems that you are reduced to inventing new names."

That is indeed true, young man.

I teach plant cell biology with a historical approach and teach "not only of the fruits but also of the trees which have borne them, and of those who planted these trees" (Lenard, 1906). This approach also allows them to understand the origins and meanings of terms; to capture the excitement of the moment of discovery; to elucidate how we, as a scientific community, know what we know; and it emphasizes the unity and continuity of human thought (Haldane, 1985). I want my students to become familiar with the great innovators in science and to learn their way of doing science (Wayne and Staves, 1998, 2008). I want my students to learn how the scientists we learn about choose and pose questions, and how they go about solving them. I do not want my students to know just the results and regurgitate those results on a test (Szent-Györgyi, 1964; Farber, 1969). I do not want my students to become scientists who merely repeat on another organism the work of others. I want my students to become like the citizens of Athens, who according to Pericles "do not imitate—but are a model to others." Whether or not my students become professional cell biologists, I hope they forever remain amateurs and dilettantes in terms of cell biology. That is, I hope that I have helped them become "one who loves cell biology" and "one who delights in cell biology" (Chargaff, 1986)—not someone who cannot recognize the difference between a pile of bricks and an edifice (Forscher, 1963), not someone who sells "buyology" (Wayne and Staves, 2008), and not someone who sells his or her academic freedom (Rabounski, 2006; Apostol, 2007).

Often people think that a science course should teach what is new, but I answer this with an amusing anecdote said by Erwin Chargaff (1986): "Kaiser Wilhelm I of Germany, Bismark's old emperor, visited the Bonn Observatory and asked the director: 'Well, dear Argelander, what's new in the starry sky?' The director answered promptly: 'Does your Majesty already know the old?' The emperor reportedly shook with laughter every time he retold the story."

According to R. John Ellis (1996),

It is useful to consider the origins of a new subject for two reasons. First, it can be instructive; the history of science provides sobering take-home messages about the importance of not ignoring observations that do not fit the prevailing conceptual paradigm, and about the value of thinking laterally, in case apparently unrelated phenomena conceal common principles. Second, once a new idea has become accepted there is often a tendency to believe that it was obvious all along—hindsight is a wonderful thing, but the problem is that it is never around when you need it!

The historical approach is necessary, in the words of George Palade (1963), "to indicate that recent findings and present concepts are only the last approximation in a long series of similar attempts which, of course, is not ended."

I teach my students that it is important to be skeptical when considering old as well as new ideas. According to Thomas Gold (1989),

New ideas in science are not always right just because they are new. Nor are the old ideas always wrong just because they are old. A critical attitude is clearly required of every scientist. But what is required is to be equally critical to the old ideas as to the new. Whenever the established ideas are accepted uncritically, but conflicting new evidence is brushed aside and not reported because it does not fit, then that particular science is in deep trouble—and it has happened quite often in the historical past.

To emphasize the problem of scientists unquestioningly accepting the conventional wisdom, Conrad H. Waddington (1977) proposed the acronym COWDUNG to signify the Conventional Wisdom of the Dominant Group.

In teaching in a historical manner, I recognize the importance of Thomas H. Huxley's (1853b) warnings that "Truth often has more than one Avatar, and whatever the forgetfulness of men, history should be just, and not allow those who had the misfortune to be before their time to pass for that reason into oblivion" and "The world, always too happy to join in toadying the rich, and taking away the 'one ewe lamb' from the poor." Indeed, it is often difficult to determine who makes a discovery (Djerassi and Hoffmann, 2001). I try to the best of my ability to give a fair and accurate account of the historical aspects of cell biology.

My course includes a laboratory section and my students perform experiments to acquire personal experience in understanding the living cell and how it works (Hume, 1748; Wilson, 1952; Ramón y Cajal, 1999). Justus von Liebig (1840) described the importance of the experimental approach this way:

Nature speaks to us in a peculiar language, in the language of phenomena; she answers at all times the questions which are put to her; and such questions are experiments. An experiment is the expression of a thought; we are near the truth when the phenomenon, elicited by the experiment, corresponds to the thought; while the opposite result shows that the question was falsely stated, and that the conception was erroneous.

My students cannot wait to get into the laboratory. In fact, they often come in on nights and weekends to use the microscopes to take photomicrographs. At the end of the semester, the students come over to my house for dinner (I worked my way through college as a cook) and bring their best photomicrographs. After dinner, they vote on the 12 best, and those are incorporated into a class calendar. The calendars are beautiful and the students often make extra to give as gifts.

In 1952, Edgar Bright Wilson Jr. wrote in *An Introduction to Scientific Research*, "There is no excuse for doing a given job in an expensive way when it can be carried through equally effectively with less expenditure." Today, with an emphasis on research that can garner significant money for a college or university through indirect costs, there is an emphasis on the first use of expensive techniques to answer cell biological questions and often questions that have already been answered. However, the very expense of the techniques often prevents one from performing the preliminary experiments necessary to learn how to do the experiment so that meaningful and valuable data and not just lists are generated. Unfortunately, the lists generated with expensive techniques often require statisticians and computer programmers, who are far removed from experiencing the living cells through observation and measurement, to tell the scientist which entries on the list are meaningful. Thus, there is a potential for the distinction between meaningful science and meaningless science to become a blur. I use John Synge's (1951) essay on vicious circles to help my students realize that there is a need to distinguish for themselves what is fundamental and what is derived.

By contrast, this book emphasizes the importance of the scientists who have made the great discoveries in cell biology using relatively low-tech quantitative and observational methods. But—and this is a big but—these scientists also treated their brains, eyes, and hands as highly developed scientific instruments. I want my students to have the ability to get to know these great scientists. I ask them to name who they think are the 10 best scientists who ever lived. Then I ask if they have ever read any of their original work. In the majority of the cases, they have never read a single work by the people who they consider to be the best scientists. This is a shame. They read the work of others ... but not the best. Interestingly, they usually are well read when it comes to reading the best writers (e.g., Shakespeare, Faulkner, etc.).

Typically, the people on my students' lists of best scientists have written books for the layperson or an autobiography (Wayne and Staves, 1998). Even Isaac Newton wrote a book for the layperson! I give my class these references and encourage them to become familiar with their favorite scientists first hand. The goal of my lectures and this book is to facilitate my students' personal and continual journey in the study of life.

My goal in teaching plant cell biology is not only to help my students understand the mechanisms of the cell and its organelles in converting energy and material matter into a living organism that performs all the functions we ascribe to life. I also hope to deepen my students' ideas of the meaning, beauty, and value of life and the value in searching for meaning and understanding in all processes involved in living.

I thank Mark Staves and my family, Michelle, Katherine, Zack, Beth, Scott, my mother and father, and aunts and uncles for their support over the years. I also thank my colleagues at Cornell University and teachers at the Universities of Massachusetts, Georgia, and California at Los Angeles, and especially Peter Hepler and Masashi Tazawa, who taught me how to see the universe in a living cell.

Randy Wayne
Department of Plant Biology, Cornell University

Preface to the Second Edition

The first edition of this book emphasized the great ideas regarding what makes life possible on the cellular level and the great observations and experiments that stimulated, supported, and challenged those ideas. That is, the first edition emphasized the questions asked by great thinkers to understand what life is and the observations and experiments performed by great observers and experimentalists to provide answers to those questions. It was an inquiry into the origin, certainty, and extent of our cell biological knowledge and left room for further questioning and wonder. Scientific inquiry not only begins with wonder but also usually ends with it too. The questions are eternal and the answers are provisional—becoming fleshed out and sometimes changed over time. Extensive references were given so that the reader could read the original papers and develop a personal relationship with the scientists who came up with the great observations, experiments, and ideas. My goal was to facilitate the prospect that the reader would be inspired to join a century-long collaboration with the scientists who wrote the original papers. Even if the reader did not join a century-long collaboration, he or she would not only be informed from reading the original references, meaning that the reader would know that something was the answer; but also, the reader would be enlightened, knowing why something was the answer. This goal was the scientific equivalent of Mortimer Adler's (See Adler and van Doren, 1967) philosophy that drove him to edit the "Great Books of the Western World" series and write "How to Read a Book."

Biology has now become systems biology. The approach of systems biology (Cullis, 2008) *"is to accumulate information and biological resources relating to as much of the genome as possible and then determining which parts are of importance."* Moreover, the questions and answers obtained in the past are often considered biased and perhaps unworthy of study. According to Sheth and Thaker (2014), *"the main challenge confronting the field is not to look back (incorporating previous findings is critical but will be comparatively easy) but to look forward to how one might plan and interpret the enormous new data that soon will be generated."* Technology is being developed to obtain big data at the systems biology level that is unbiased. However, recognizing what bias is and what wisdom and knowledge are depends on an ability to read the relevant papers, the ability to work with one's eyes and hands to make observations and do experiments, and the ability to understand the ideas, observations, and experiments. This edition maintains and updates the philosophical outlook of the first edition, emphasizing how we know what we know, so that the reader can come to his or her own conclusion about the value of the work.

This edition also includes a new chapter entitled, Omic Science: Platforms and Pipelines, which emphasizes the great ideas and experiments that provided the basis for the technologies used in systems biology. I emphasize the development of the technologies rather than the results obtained from the technologies, as a study of the development of the technologies reveals real scientific achievement and creativity, and the explanation of their development has real pedagogical value. On the other hand, the results produced by the technologies are by necessity wanting given that the goal is to characterize everything in an unbiased manner (Chory et al., 2000), and, at the present time, we are as close to knowing nothing new from the systems approach as we are to knowing everything.

According to Bruce Alberts, Marc Kirschner, Shirley Tilghman, and Harold Varmus (2012) *"the system now favors those who can guarantee results rather than those with potentially path-breaking ideas that, by definition, cannot promise success. Young investigators are discouraged from departing too far from their postdoctoral work, when they should instead be posing new questions and inventing new approaches. Seasoned investigators are inclined to stick to their tried-and-true formulas for success rather than explore new fields."* Where is the freedom to think? Not only are trained scientists working like automatons but also being replaced by automatons. According to Steve Strogatz (Manjoo, 2011), *"Our time is limited. As thinking machines, they have a lot of advantages over us—this is obvious... We're not going to be the best players in town. I do think we'll be put out of business. This is really going to happen."*

More importantly, I'd like to ask the question: What are the goals of science? Are the goals best done by computers? Or should the goals be based on the proposition that science is a field of human endeavor that promotes freedom by training people to think. John Dewey (1910) realized, *"Genuine freedom, in short, is intellectual; it rests in the trained power of*

thought, in ability to 'turn things over,' to look at matters deliberately, to judge whether the amount and kind of evidence requisite for decision is at hand, and if not, to tell where and how to seek such evidence. If a man's actions are not guided by thoughtful conclusions, then they are guided by inconsiderate impulse, unbalanced appetite, caprice, or the circumstances of the moment. To cultivate unhindered, unreflective external activity is to foster enslavement, for it leaves the person at the mercy of appetite, sense, and circumstance." We have to take seriously what Marcus Garvey (1938) said in a speech given in Nova Scotia, "We are going to emancipate ourselves from mental slavery because whilst others might free the body, none but ourselves can free the mind." Bob Marley immortalized these words in *Redemption Song*.

The culture of scientific research is in danger of eliminating what is necessary to cultivate the intelligent and creative use of technology. Both Jacobus van't Hoff (1967), who viewed chemicals in three-dimensional space, and Peter Mitchell (1980), who viewed metabolism in three-dimensional space as well as time, quoted Henry Thomas Buckle's (1872) description of the type of imagination needed to make great scientific discoveries: "there is a spiritual, a poetic, and for aught we know a spontaneous and uncaused element in the human mind, which ever and anon, suddenly and without warning, gives us a glimpse and a forecast of the future, and urges us to seize the truth as it were by anticipation." Yes, serendipity favors a prepared mind.

This book is written for the students who are craving to be free to do curiosity-driven science that requires thinking, imagination, and skill. It is also written for the taxpayer who expects their hard-earned money to be invested wisely. It is my hope that this book will help turn the scientific pendulum back so that science can once again encourage a way of understanding nature that is fueled by the intelligent use of technology and the scientific imagination (Holton, 1978).

I wrote the following paragraph in the Preface to the First Edition:

In 1952, Edgar Bright Wilson Jr. wrote in *An Introduction to Scientific Research*, "There is no excuse for doing a given job in an expensive way when it can be carried through equally effectively with less expenditure." Today, with an emphasis on research that can garner significant money for a college or university through indirect costs, there is an emphasis on the first use of expensive techniques to answer cell biological questions and often questions that have already been answered. However, the very expense of the techniques often prevents one from performing the preliminary experiments necessary to learn how to do the experiment so that meaningful and valuable data and not just lists are generated. Unfortunately, the lists generated with expensive techniques often require statisticians and computer programmers, who are far removed from experiencing the living cells through observation and measurement, to tell the scientist which entries on the list are meaningful. Thus, there is a potential for the distinction between meaningful science and meaningless science to become a blur.

In this preface, I would like to update the paragraph by substituting "Facilities & Administrative (F&A) costs" for "indirect costs."

I would like to heartily thank Mohanapriyan Rajendran for finding so many of my mistakes, typos, and omissions. Lastly, I would like to thank Karl Niklas, a scholar and a gentleman, for the fascinating and thought-provoking conversations we have about biology and teaching every morning.