CHAPTER 2

CHANGING IDEAS ABOUT CELLS AS COMPLEX SYSTEMS

Jane Maienschein

As Edmund Beecher Wilson finished writing the third and final edition of his *The Cell in Development and Heredity*, he noted that in the future probably no single author could write such a cell biology text. The subject had become too complex and required too many different kinds of expertise to do it justice. About the same time, Wilson joined Edmund Cowdry and other leading biologists in a workshop at the Marine Biological Laboratory (MBL), where the distinguished group divided up the topics to write the collective 1924 volume *General Cytology* (Wilson 1925; Cowdry 1924). Cowdry then convened a larger and even more diverse group to produce two volumes on *Special Cytology* (Cowdry 1928; Cowdry 1932).

Far from being of merely antiquarian interest, these volumes reveal underlying assumptions that both reflected and informed the directions of scientific research. The 1924 Cowdry volume focused on the architecture and activities of individual cells, not primarily as building blocks of living organisms but also as the fundamental units that were themselves living, and the authors emphasized the value of studying these living cells in detail. The group clearly saw the beginning of a new field of cell biology emerging, one that might lose the coherence of a single approach but gain from different points of view, using different techniques to ask different questions about complex cells and their activities.

This chapter looks at the context in which Cowdry's volume appeared, a context constructed on the foundation of the first cell theory of 1839 and subsequent developments. The story leads to questions about what the Cowdry volume tells us about the science of understanding cells more generally. It looks at what the 1924 volume offers in seeing cells as having gained autonomy, integrity, and biological importance as complex living systems in their own right. In addition, some of the chapters and reviews focus on understanding that the individual cells work together to make up complex organisms, such that organization arises through their connections. Yet the chapters mostly remain focused on the individual cells themselves rather than on how they communicate with each other and work as a whole. The Cowdry volume presents an American story, focused on Woods

Hole at a time after World War I when scientists in the United States aspired to scientific leadership. To gain perspective on the contributions of Cowdry's volume, it is useful to start briefly at a prominent discussion at the centennial of the cell theory for a broader view looking back, and then to move on to *General Cytology* itself.

Reflecting on the First Century of Cell Theory

In his introduction to the centennial volume entitled *The Cell and Protoplasm* in 1940, editor Forest Ray Moulton noted that the American Association for the Advancement of Science was publishing the book as part of a series. It grew out of a symposium, held in 1939, to celebrate the centennial of Matthias Schleiden and Theodor Schwann's introduction of the scientific cell theory. Because of the rich history of thinking about cells up to that time, Moulton felt that "in a sense the Cell Theory is not new." Yet, he continued, "In another sense the Cell Theory is always new, for every discovery respecting this primary and essential unit of living organisms, both plant and animal, has raised more questions than it has answered and has always widened the fields of inquiry" (Moulton 1940, "Foreword"). The volume set out to show both what was old and well established and what was new a century after the original idea of cells.

By 1940, discussion of cells usually separated plant, microbial, and animal cells. For plants, discussion typically involved looking at such predictable topics as cell walls, while discussion of animal cells looked more closely at delineation of individual cells; contents of cells, including nucleus, cytoplasm, and organelles; and environments, both internal and external to each cell. Along the way came considerations of biochemistry and cell physiology. More surprising in the 1940 volume are the less standard chapters on microbiology, viruses, enzymes, hormones, and vitamins. The choice of topics and of contributors makes clear just how much remained in 1940 to be discovered about cells and especially about the ways they interact with each other as well as with their environment. The contributors realized that they still knew relatively little about how the individual cells add up to an organized, whole, complex organism, though they recognized that the process of making coordinated combinations of parts was key to understanding living systems and organisms.

We see this emphasis on individual cells in textbooks of the time as well. For example, Lester W. Sharp's very widely used *Fundamentals of Cytology* of 1943 (as well as other editions) laid out the way that cytoplasm and nucleus work in the cell, looked at different kinds of cells, and recognized that cells make up organisms, but had relatively little to say about the latter point. Sharp noted that in addition to the cell theory focused on the cells themselves, other researchers had a different view of living organisms that supported an emphasis on each organism as a whole. The two different perspectives have to come together in some way, Sharp recognized, for "in every normal mass of protoplasm, whatever its growth pattern or degree of differentiation, the many diversified activities are so coordinated that it behaves as a consistent whole, or individual, from the beginning of development onward; without such harmony there obviously could be no organism" (Sharp 1943, 20). Yes, but how could this harmony be achieved?

The connections were not yet clear. Some biologists continued to look at organisms as organized living systems that happen to consist of cells, while others looked at aggregations of cells as making up organized living systems. At issue was partly a matter of emphasis, but also partly a matter of causal efficacy. Do cell divisions and actions cause organisms, or does some integrated wholeness cause cells to behave as they do? What drives the integration of the whole organism? These were still questions in the 1940s, and the discussion shows that biology had not embraced a single "cell theory" to explain the basis for all living systems.

Sharp explained that cell structure and function affect or perhaps even effect the organism, but it remained unclear just how that happens. In an earlier picture of cells as structural units or building blocks, it was easier to treat them like bricks or stones that combined into a larger organism through forces outside the cells themselves. But if cells were each living units in their own right, then how do all those separate cells relate to the organism as a whole, and how do they make up that whole? How could new research resolve persistent debates? In particular, by the end of the nineteenth century, in the face of increasing knowledge about protoplasm and internal workings of cells, which theory about life should hold? "The proponents of the cell theory stressed the cell as the primary agent of organization, while adherents of the organismal theory insist upon the primacy of the whole, cells when present being important but subsidiary parts" (Sharp 1943, 21). Furthermore, looking at evolutionary relationships by comparing studies of different organisms suggested that a different kind of protoplasm might serve to connect cells and might thereby help to bring together coordinated whole organisms in somewhat different ways and not necessarily in exactly the same processes and patterns for each kind of organism. Many questions remained in 1940, including questions about what cell theory was and how it had changed over time.

Again, this work of the mid-twentieth century reinforced just how much had been learned about the details of cells, and yet how little that knowledge revealed about the ways cells work together in a coordinated way in more complex animals. It is worth looking at how the science had gotten to this point. The history of cell biology shows a first stage of thinking about cells as the structural units of living organisms, followed by a stage of thinking about cells as themselves more nearly the "agent[s] of organization," as Sharp put it. Reflecting on the development of cell theory took Sharp, Cowdry's group, and takes us as well, to previous studies of cells, starting with Schleiden and Schwann.

In the Beginning

Most of us have heard something about the basic story of Schleiden and Schwann and the cell theory that they invented, which is recounted in textbook after textbook—except that we do not know the historically accurate story, because the textbooks usually get it wrong, or partly wrong. Those accounts tell of these two German innovators, one working on plants and the other working on animals, as coming up with *the* theory that cells are the fundamental units of life. The story goes that these two began to put together the available evidence and reasoning to develop what they called the *Zellenlehre* and what others labeled the *Zellentheorie* that has grounded all of biology since (Schwann 1839).

Everybody likes a good myth, and like most, this one is not completely inaccurate. Matthias Schleiden and Theodor Schwann did, respectively, study plants and animals and did see and describe structural units that they called cells. Their work added to earlier observations by Robert Hooke, Anthony Leeuwenhoek, and others to establish the idea of structural cellular units as bounded by walls and consisting of some internal fluid-like or gel-like substance. The claim that they established cell theory in the sense that the cell is the fundamental unit of life, or the fundamental living unit, is less clear.

In the mid-twentieth century, several biologists looked much more closely at the historical record and at what each contributor to the foundational biological idea had actually done. They began to replace the earlier, oversimplified interpretations. In 1948, the Oxford University cytologist John Randal Baker began a series of essays in the *Quarterly Journal of Microscopical Science*. Under the title "The Cell-Theory: A Restatement, History, and Critique," Baker reported on his close studies of the primary sources that textbooks had so frequently mentioned but seldom studied in any detail. He began his essays with the point that "several zoological text-books published during the last two decades have cast doubts on the validity of the cell-theory." Baker resolved to review the recent attacks, the nature of the evidence, and to establish the current status of the cell theory. He found that different critiques were attacking different aspects of what was lumped into the cell theory, and he found some of the attacks were justified, while others were not—largely because the critics were really talking about different things (Baker 1948, 103).

Baker broke down the larger cell theory into seven propositions, then explored each in turn. They involved claims that (1) most organisms consist of microscopic cells, (2) cells have definable characters, (3) cells usually come from other cells, (4) cells are the living parts of organisms, (5) cells are individuals, (6) cells are like living protists, and (7) many-celled organisms may have resulted from protists coming together. And his discussion focused on the shape, characteristics, origin, development, individuality, and claims about the relationships of multiple cells in multicellular organisms (Baker 1988, 107).

Through his five essays, Baker provided a tremendous service in clarifying what was at issue in discussions of cell biology. He showed that Schleiden and Schwann each, in different ways, made assumptions about how cells originate or about their structure and nature that went beyond their data from what they could observe. In some cases, they worked with inadequate microscopic tools; in other cases, they started with views about what they should see and then somehow became convinced that they had actually seen it—whether it was really there or not. In particular, Schwann was confident that he saw cells forming around a nucleus, much as crystals form from inorganic matter. Baker's essays appeared from 1949 to 1955, and his careful research showed very clearly who had said and thought what, when, and why.

Shortly after, in 1959, Cambridge University anatomist Arthur Hughes published *A History of Cytology*. Like Baker, and probably for some of the same reasons related to questions about the cell theory at the time, Hughes sought to clarify the development of the understanding of cells. Hughes emphasized the cytological methods of investigation alongside the theories, with special emphasis on the nucleus and the cytoplasm (Hughes 1959).

Each of these mid–twentieth century historical studies focused on cell structure and asked how we came to the idea that cells are the fundamental structural units of living organisms. Textbooks of the time reinforced the underlying view that cells do, in fact, play this central role, thereby reinforcing some version of a cell theory. Yet Moulton's question from 1940 remained: Do the cells themselves serve as the drivers for development and organization, or are cells instead the results of the process of organismal development. To put it another way: To what extent, and in what ways, are cells the units of life rather than simply the structural units of living systems? A century after the introduction of the cell theory, this question had not yet been answered.

Cells as Structural Units of Living Organisms

For many who saw Schleiden and Schwann as the beginning for cell theory, those two gave cell theory a name. They declared, first, that cells exist and are constituents of living organisms and, second, that the theory might help to explain the individuality of more complex organisms that consist of multiple cells. The decades following brought a great deal of additional observation as well as interpretation. Those years also brought improvements in both microscopes and microscopic techniques, as Hughes discussed in some detail. In studying cells, what one can see and how well one can see it are of crucial importance; and making sure that others can see the same thing is especially important. Better lenses reduced chromatic aberration, and better fixing, staining, and sectioning methods brought consistency to the preparation of specimens (Bracegirdle 1978). The whole story is much richer than this, and a number of historians of science have taken up aspects of early cell theory. In addition, as Jutta Schickore explains in chapter 4 of this volume, the technical innovations brought additional questions of interpretation. The emphasis here is on the emerging understanding of cells that informed the 1924 Cowdry volume, to help us interpret the contribution and impact of that volume.

In 1834, Karl Ernst von Baer had presented observations of frog cleavage stages, which clearly showed what later biologists saw as cells dividing, each reliably dividing in the same way and following the same basic patterns, or what were later called lineages of cell divisions within the organism. Von Baer's images were also taken as showing that the full material in the initial egg divides into more and more cells, which remain separate. His illustration clearly supported a claim that the collection of cells is what makes up the developing organism—not intercellular connections or noncellular material (von Baer 1834). The images were taken as representing division into separate structural units, and for those who held that those units were cells, they played an important structural role.

Yet not everybody accepted cells as having such a role, especially those who focused on organisms as a whole. Historian Marsha Richmond points to Thomas Henry Huxley as a leading critic, and she argues that he rejected cell theory in part because it seemed to assign the cells a sort of preformationist role, as if the cells themselves cause development and body structure. Huxley held a more epigenetic view. As Richmond notes, Huxley insisted that cells are "not instruments, but indications—that they are no more the producers of the vital phenomena than the shells scattered in orderly lines along the sea-beach are the instruments by which the gravitative force of the moon acts upon the oceans. Like these, the cells mark only where the vital tides have been, and how they have acted" (Richmond 2002, citing Huxley 1853). Richmond further discusses the debates of the time, which make clear that cell theory was not a clearly defined, unified, or universally accepted idea. (See also Whitman 1893 on what he called "the inadequacies of the cell theory.")

In fact, one main alternative idea persisted, affirming that some sort of protoplasm lies outside the cells and connects them. Huxley put forth such ideas. Adam Sedgwick was still invoking this idea through the end of the nineteenth century, as Baker discusses at greater length (Baker 1988, 175; Sedgwick 1894). The idea of a reticulum, or syncytial connections, proved attractive because it seemed to offer an explanation for how the cellular parts might work together as an organismal whole. Physical connections make the parts into a network. The same reasoning held for the nervous system. At the end of the nineteenth century, researchers argued about whether the nervous system is there from the very beginning in a sort of reticulum that then grows larger while maintaining its structure (Billings 1971). This idea of a protoplasmic reticulum could explain how the complex structure arose and was maintained. In contrast, the neuronal theory held that individual neuroblast cells then develop nerve fibers that grow out and make connections. Gradually, they extend, develop connections, and make up the nervous system.

Some researchers, such as Ross Granville Harrison, could easily imagine how such a complex system can arise from the interactions of individual cells. His study of individual cells led him to develop the first successful tissue culture and the first stem cell research, with transplanted neuroblasts (neural cells). Harrison's work was taken by many as having resolved the question in favor of the action of individual cells working together. Certainly Santiago Ramon y Cajal agreed. In contrast, Ramon y Cajal's corecipient of the Nobel Prize, Camillo Golgi, and others never gave up their convictions that the system was inextricably interconnected from the beginning. The discussions were part of persistent debates about whether development is more preformationist, that is laid out from the very beginning in a preformed way, or epigenetic, that is arising only gradually over time. These debates have been discussed in detail elsewhere, and we need not repeat the entire story here (Maienschein 1983; Maienschein 1991).

It is worth remembering that when different people looked at cells, some saw them as newly arisen objects making up an organism, and some saw them more as products of cell division from past cells. Both are partly true, and it really depends on how one does the looking and what one is looking for. It depends, as is so often the case, on perspective.

The former, epigenetic view requires an explanation for how the individual cells arise and how they make up a whole organism. Where does the organization and where does the life come from if the separate and individual cells come together only gradually over time to make a whole? The temptation was strong to invoke some form of teleological or vitalistic principle or force to offer such an explanation and drive the process. Aristotle had given us two and a half millennia of thinking in such gradual, epigenetic terms, and his instincts fit with those of many other observers. While later thinkers discarded Aristotle's entelechy, they had to find explanations for the emergence of form and function in some other way (see Maienschein 2011).

In contrast, if cells arise only from other cells, then the "life" and the beginnings of the form are in some sense already there from the beginning. Thus, when Robert Remak showed that cells divide and give rise to other cells, and Rudolf Virchow famously declared that "*omnis cellula e cellula*," their assertions that cells come from other cells were clear and direct. The claim was neither entirely new, however, nor was it universally accepted at the time. Asserting that cells come from other cells pushes back the explanation of where they come from in the first place as well as the question of how they come to be "alive." If cells are the fundamental unit of life, and more than just the structural building blocks of living things, then how so? And what follows for our understanding of biological processes? (See Maienschein 2014, chap. 1.)

Cells as Living Units

This very quick look at leading ideas brings us to the end of the nineteenth century and to the work of Theodor Boveri, Oscar Hertwig, and Edmund Beecher Wilson. A number of researchers had demonstrated that the cell has structure, with a distinct bounded nucleus, liquid or gel-like cytoplasm, and other structures including the mitochondria and Golgi bodies, with spindle fibers, asters, and centrosomes playing important roles during cell division. Again, historians have covered this period in detail, and the rich historical work of cell biologist Sir Henry Harris at the University of Oxford provides the best modern account in *The Birth of the Cell*, which appeared in 1999.

Harris goes over much of the same ground as Baker and Hughes, but with considerably more interpretive subtlety. He has reread the original sources, and furthermore has the benefit of an additional half-century of biological discovery and reflection on our understanding of cells. Harris frames his work with a selected quotation from the French microscopist François-Vincent Raspail: "Give me an organic vesicle endowed with life and I will give you back the whole of the organized world." Making the claim that the German story came to dominate—and perhaps to distort—the history of cell biology as well as the work of cytology itself, Harris calls for recognizing the alternative point of view held by Raspail and a few others. While most of those studying cells were still focused on establishing all the details of structure, Raspail already by the early nineteenth century saw the cell as a "kind of laboratory" that allowed development of the life of an organism out of the life of the individual cells (Raspail 1833; Harris 1999).

Understanding life also involves sorting out what is going on with heredity and development. By the last quarter of the nineteenth century, Oscar Hertwig provided a widely cited solidification of the accumulating evidence and reasoning about the nature of fertilization, concluding that the nucleus of the egg and sperm come together to make a new nucleus for the zygote. This provided the starting point for a new cell. Efforts to understand whether chromosomes retain their individuality throughout cell divisions, and whether they retain all their material or undergo some sort of reduction division occupied Hertwig's attention and led to greater clarity of what the questions were surrounding fertilization and cell division. As Harris discusses, a number of other researchers also began to ask similar questions directed at understanding the cell as a living functional unit. In particular, they wanted to know how each cell grows, divides, differentiates, and otherwise changes over time in ways that add up to a complex organized organism?

Theodor Boveri provided some answers, looking closely at the contributions of the nucleus. In 1902, for example, Boveri demonstrated that chromosomes are defined structures and, furthermore, that they retain their individuality through cell divisions. They divide in such a way that each of the daughter cells has its own set of chromosomes after divisions, but they retain their individuality nonetheless. Observing carefully both naturally occurring and experimentally derived examples, Boveri added immeasurably to the understanding of cell division with his experimental work.

Manfred Laubichler and Eric Davidson have suggested that Boveri was thinking in very forward-looking terms about the cell and the roles of its parts. They help us see Boveri as a visionary able to imagine something conceptually similar to today's complex organisms guided by gene regulatory networks, even though Boveri thought of them as determinants on chromosomes in the nucleus and did not yet have a concept of genes specifically (Laubichler and Davidson 2008).

Cells as Complex Living Systems: Wilson's *The Cell*

Edmund Beecher Wilson built on the work of Hertwig, Boveri, and many others. For Wilson, the cell plays a foundational role for life and therefore also for the study of life through biology. Wilson's work influenced generations of cell and developmental biologists because of the way he brought together and made sense of so many different pieces of evidence about parts of the cell and its changes over time. In the first 1896 edition of his classic textbook, entitled *The Cell in Development and Inheritance* and dedicated to Boveri, Wilson opened his introduction by pointing to Schleiden and Schwann: "During the half-century that has elapsed since the enunciation of the cell-theory by Schleiden and Schwann, in 1838–39, it has become ever more clearly apparent that the key to all ultimate biological problems must, in the last analysis, be sought in the cell." Furthermore, "No other biological generalization, save only the theory of organic evolution, has brought so many apparently diverse phenomena under a common point of view or has accomplished more for the unification of knowledge. The cell-theory must therefore be placed beside the evolution-theory as one of the foundation stones of modern biology" (Wilson 1896, 1). He saw his task in part as bringing the two together, showing the role of cells in development and heredity, in ways that made evolution possible.

By the third and final edition in 1925, Wilson acknowledged that a great deal had changed—the volume had grown from 371 to 1232 pages and had undergone reconceptualization while seeking to retain its synthetic approach. For that last edition, he opened with a slightly different tone: "Among the milestones of modern scientific progress the cell-theory of Schleiden and Schwann, enunciated in 1838–39, stands forth as one of the commanding landmarks of the nineteenth century." Yet he went on to note that their ideas were just a "rude sketch" and that it nonetheless succeeded in "opening a new point of view for the study of living organisms, and revealing the outlines of a fundamental common plan of organization that underlies their endless external diversity" (Wilson 1925, 1).

In this third edition, Wilson pointed to three rough periods since the inception of the initial idea of cells: the first focused on the basic ideas about cells and their roles; the second looked at development and cell division; and the third brought in the chromosome theory of heredity, which introduced explanations of the causes of cell division. This third period had made heredity more a matter of biochemistry and metabolism, Wilson thought (Wilson 1925, 1114). Wilson pointed to several key phenomena that remained puzzles, concluding that "we are still without adequate understanding of the physiological relations between nucleus and cytoplasm and of the manner in which the nucleus is concerned in the operations of constructive metabolism, of growth and repair, and in the determination of hereditary traits. The same may be said of our present knowledge of development, above all in respect to the problem of localization." Further, he asked, "What determines the appearance of hereditary traits in regular order of space and time? How are the operations of development so coordinated as to give rise to a definitely ordered system?" (Wilson 1925, 1115). And how can a proper understanding in physicochemical terms of the "organization" of the organism push away any temptations toward vitalism that he found in some of his contemporaries?

In the third edition also, even more than in the previous two, he ended by pointing to the successes of recent years in moving forward on all three contributions, while acknowledging that many questions remained. "If we are confronted still," he wrote in the final paragraph, "with a formidable array of problems not yet solved, we may take courage from the certainty that we shall solve a great number of them in the future, as so many have been in the past" (Wilson 1925, 1118).

Senior scholars today recall buying this last edition of Wilson's book and reading it for one or another class, as well as being instructed to keep the volume nearby for reference. With his series of three editions of *The Cell*, Wilson provided a compendium of existing knowledge about cells and the ways that they reflect the processes of life. His message was that each cell is a fundamental living unit, useful for understanding the processes of life as well as the structure of living organisms. Interpreting those processes, though, required bringing together heredity, development, and evolution.

Wilson provided a view of the cell as an individual, complex, living system. The year before his first edition in 1895, he had published *The Atlas of Fertilization and Karyokinesis of the Ovum*, which included a set of beautiful print copies of photographs taken of the early stages of fertilization and cell division. Collaborating with photographer Edward Leaming, Wilson sought to show his readers the complex parts of the cell and how they change during those early stages. By 1896, he provided considerably more detail about later roles of the cell as well. His point in the *Atlas* was precisely to provide an atlas, a sort of collection of maps of structures.

The Cell added function and development. In the process, the cell came alive. Cells still went through stages of development, but Wilson sought to capture more than the standardized stages characteristic of normal tables. He wanted to understand more about what it meant to be alive and especially what it meant to be organized into an individual organism with integrity and autonomy. What Wilson did not quite see yet, despite his clarity of vision and depth of understanding, was the importance of understanding the ways in which cells interact with other cells and the complexity of the regulatory processes that reside within the inherited material but go beyond each individual cell itself.

Edmund Cowdry, *General Cytology*

As Wilson had acknowledged, and despite his attempts to provide a summary update of the field with his own third edition, by 1924 the challenges of understanding the cell had already grown beyond what any single researcher could grasp. Indeed, the very brief summary of ideas taken to be important leading up to 1924 has focused especially on parts of the story about study of cells. Other researchers were looking more intently at physiology, biochemistry, and other areas that fed into the study of cells, especially in later periods. The point here has been to put us at least partly inside the thinking of those who gathered to produce the volume edited by Cowdry.

By 1924, the biologists who gathered to produce the edited volume agreed that it was time for a cooperative approach, which Edmund Cowdry coordinated at the Marine Biological Laboratory in Woods Hole (see also the introduction to this volume). Cowdry noted that, because contributors had worked in the MBL facilities, "the volume, as it stands, is to be considered, to some extent at least, as a contribution from the Marine Biological Laboratory" (Cowdry 1924, v).

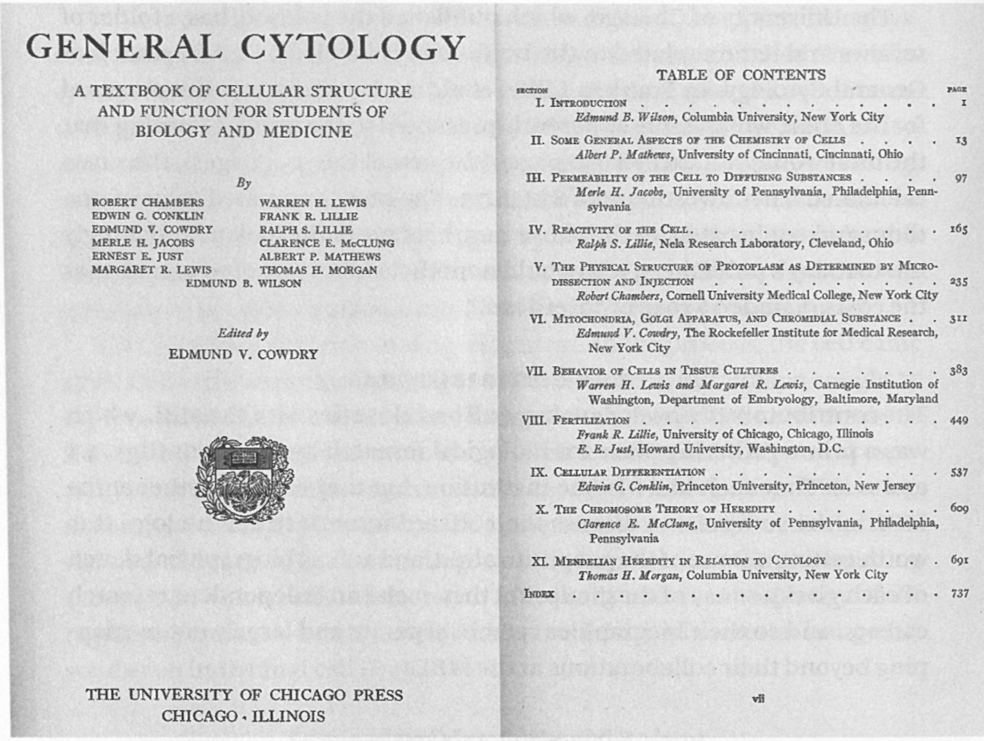
The University of Chicago, which published the volume, has a folder of reviews and letters related to the book. One is labeled "17. A Textbook of General Cytology. By Frank R. Lillie, et al." and summarizes the proposal for the book, which Lillie apparently presented to the press. Claiming that the total would not exceed 650 pages (the actual was 754 pages), the press calculated a net investment of $3436.75. The press estimated sales of one thousand copies at $5 each. Those numbers probably look astonishingly low to today's publishers, who would nonetheless be reassured to note that the costs included $1010 of "overhead."

THE CONTRIBUTORS

The contributors to Cowdry's volume all had close ties with the MBL, which was a prime gathering place for biological research by the 1920s (figs. 2.1 and 2.2). They each had a home institution, but they came together at the MBL in the summers to discuss their shared interest in cell biology. It is worth getting a sense of the people involved, and a short biographical sketch of each gives a sense of the group. Yet they each had independent research careers, and so their biographies remain separate and largely not overlapping beyond their collaborations at the MBL.

Edmund Vincent Cowdry

Edmund Vincent Cowdry was born in Alberta, British Columbia, in 1888, the same year that the MBL opened its doors. Cowdry received his Bachelor's degree from the University of Toronto and a PhD from the University of Chicago. He moved to the Johns Hopkins University in anatomy and in 1916 married Alice Hanford Smith, going to the MBL for summer research. A year later, the China Medical Board of the Rockefeller Foundation recruited Cowdry to establish and lead an Anatomy Department of Peking Union Medical College in Beijing, and he and Alice moved there in 1917. With the birth of their first child in 1920, Cowdry returned to the United States to the Rockefeller Institute in New York and studied a range of topics, including anatomy, cytology, parasitic diseases, and aging. He continued to spend many summers at the MBL and to establish his editorial credentials. Cowdry took up an academic position at Washington University in St. Louis in 1930. There, he moved increasingly to studies of aging while continuing to focus on cytology, looking at cell degeneration in particular. As Hyung Wook Park has shown, Cowdry became a leader in gerontology and organized a conference on aging at the MBL in 1937, which was supported by



GENERAL CYTOLOGY

A TEXTBOOK OF CELLULAR STRUCTURE AND FUNCTION FOR STUDENTS OF BIOLOGY AND MEDICINE

By

ROBERT CHAMBERS
EDWIN G. CONKLIN
EDMUND V. COWDRY
MERLE H. JACOBS
ERNEST E. JUST
MARGARET R. LEWIS
WARREN H. LEWIS
FRANK R. LILLIE
RALPH S. LILLIE
CLARENCE E. McCLUNG
ALBERT P. MATHEWS
THOMAS H. MORGAN
EDMUND B. WILSON

Edited by
EDMUND V. COWDRY

THE UNIVERSITY OF CHICAGO PRESS
CHICAGO · ILLINOIS

TABLE OF CONTENTS

vii

Figure 2.1. The title page and table of contents from Cowdry's *General Cytology*, as published in 1924.

the Josiah Macy Jr. Foundation and is considered the first such scientific meeting (Park 2008; 2016).

Edmund Beecher Wilson

Edmund Beecher Wilson was the leading cell biologist of the day and a senior statesman. Born in Geneva, Illinois, in 1856, young Wilson enjoyed learning about natural history. He received a PhB degree from Yale University in 1875 and proceeded to the new Johns Hopkins University for a PhD under William Keith Brooks. After a visit to Germany and the Naples Zoological Station, Wilson spent a year at Williams College, then visited at MIT, where he wrote a biology textbook with his fellow Hopkins graduate William Sedgwick, and in 1885 he took a position as head of the biology department at the new Bryn Mawr College for Women. In 1891 Wilson moved to Columbia University, where he remained for the rest of his career,

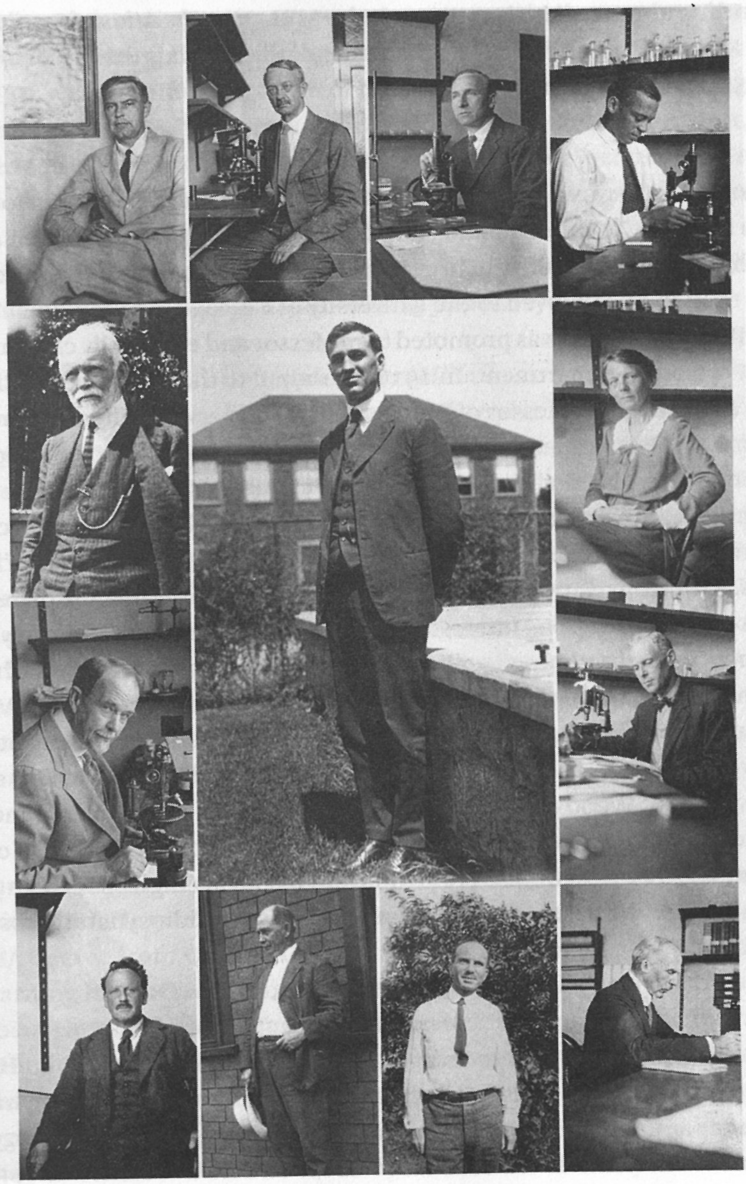


Figure 2.2. The contributors to *General Cytology*, as pictured in the 1920s. Edmund Cowdry, the editor, is in the center. Others include (*clockwise from the top left*) Robert Chambers, Edwin Conklin, Merle Jacobs, Ernest Just, Margaret Lewis, Warren Lewis, Frank Lillie, Ralph Lillie, Clarence McClung, Albert Matthews, Thomas Hunt Morgan, and E. B. Wilson. Images reproduced from the website "History of the Marine Biological Laboratory" (http://hpsrepository.asu.edu/).

spending almost all his summers at the MBL. His *The Atlas of Fertilization and Karyokinesis*, and *The Cell* set the standard, as discussed earlier (Wilson 1895; 1896; Morgan 1940).

Albert P. Mathews

Albert P. Mathews was born in 1871 in Chicago. He received a Bachelor's degree from MIT, studying biology under William Sedgwick, and then a PhD from Columbia University. He taught first at Tufts College Medical School, and then in 1901 moved to the University of Chicago, where he remained for fifteen years and was promoted to professor and eventually chairman of the Physiology Department. In 1916, he moved to the University of Cincinnati as Carnegie Professor of Biochemistry, and served as head of the Biochemistry Department until he retired in 1939. Though his work focused on chemistry, he also pursued physics in relation to life and wrote work on gravity, matter, space-time, and such topics. Mathews began his career looking at the biochemistry of secretions, but soon moved to study of living cells. E. Newton Harvey explained that "Woods Hole was just the place for a man of Mathews' broad interests, and the group benefited immensely from his new and stimulating ideas." That group, living near Mathews's house on Buzzards Bay Avenue, included Thomas Hunt Morgan next door, Wilson across the street, Conklin and Jacques Loeb nearby, among many others. Harvey recalled, "I can still see him, walking briskly with great strides along the streets of Woods Hole, with his head held high and a keen penetrating look in his blue eyes, as if he were about to lay bare the secrets of the universe. His convictions were strong and his ideals high" (Harvey 1958a, 744). We see those strong convictions in his highly idiosyncratic essay in the Cowdry volume.

Merkel H. Jacobs

Merkel H. Jacobs was born in 1885 in Harrisburg, Pennsylvania. He received his Bachelor's and PhD degrees from the University of Pennsylvania, and after a year in Berlin, he returned to the university in protozoology. He spent the war years in the Sanitation Corps and then returned to Penn in 1921, remaining there until he retired in 1955. A memorial by Warner E. Love reported that "he was tenacious of purpose, very hard working, high-principles, and kept his own council. He spoke ill of no one. To those around him, he was above all, gentle" (Love 1971, 16). Shortly after Cowdry published his collaborative volume, Jacobs became the third director of the MBL. He had been a member of the MBL Corporation since 1911 and became associate director in 1925–1926 and then director from 1926–1938, while also directing the physiology course. The 1920s was a lively time for the MBL, with significant growth of the physical facilities and increasing numbers attending the courses and carrying out research. In contrast, the Depression of the 1930s brought serious challenges that Jacobs had to navigate to keep the institution afloat. That he nonetheless managed to continue his studies of cell permeability and to inspire many to enter the field is evident from the dedication of a special issue of the *Journal of Cellular and Comparative Physiology* to Jacobs in 1956 (Harvey 1956).

Ralph Stayner Lillie

Ralph Stayner Lillie, was born in Toronto and received his BA from the University of Toronto in 1896 and his PhD from the University of Chicago. After that he worked at the Nela Research Laboratory in Cleveland, the Carnegie Institution of Washington at Johns Hopkins, and then at Clark University as professor of biology, with positions also at the University of Nebraska, Harvard, Johns Hopkins, and the University of Pennsylvania. In 1924, Lillie moved back to the University of Chicago as professor of general physiology until he retired in 1952. Lillie was intrigued by the dynamic activity of organisms, as reflected in his *General Biology and Philosophy of Organism*. Like his brother Frank, Ralph spent many summers at the MBL as a researcher and as a trustee (Ralph S. Lillie Papers).

Robert Chambers

Robert Chambers was born in Erzerum, Turkey, where his parents served as missionaries. He graduated from Robert's College in Istanbul and received an MA degree from Queens University in Kingston, Ontario, Canada. After earning his PhD in Munich, studying cell physiology and embryology, he spent time at the MBL, first as a researcher, then on the teaching staff, and then directing a summer cell biology laboratory at the MBL. His first academic position was in Cincinnati at the Medical College for three years, then at Cornell University Medical College in New York City until he retired in 1949. His student Irene P. Goldring noted that Chambers encouraged her to go to the MBL embryology course, which she did in 1948, and she later wrote, "My introduction to the life of that community enabled me to hear at first-hand, anecdotes and somewhat apocryphal tales of the legend that Robert Chambers had become." Chambers told Goldring that during his own introduction to embryology, he had said, "Dear God, I believe in the chromosomes, I believe in the spindle, I believe in the asters, now help me to find out what they actually are" (Goldring 1979, 1271). Chambers served as an MBL trustee and regarded summers in Woods Hole as the most important time of his year.

Warren Harmon Lewis

Warren Harmon Lewis was born in 1870 in Suffield, Connecticut, and soon moved to Chicago. He received his BS from the University of Michigan and remained as an assistant for a year. In 1896, he entered the still new Johns Hopkins University Medical School, where he became fascinated by anatomy and graduated in 1900. He studied experimental embryology with Jacques Loeb at the MBL. As his biographer George Corner put it, "A summer with Jacques Loeb could not fail to open the eyes of his young associate to the exciting possibilities of experimental cytology" (Corner 1967, 326). At the MBL, he later met Margaret Reed, whom he married in 1910, and they had three children. Margaret and Warren Lewis worked closely in their shared research, carrying out tissue and cell culture studies designed to observe and document cell movements under different conditions. They improved culture media, made videos of developing cells, and continued exploring movements in living cells. In 1917, Warren Lewis moved to the Carnegie Institution of Washington's Department of Embryology, which was on the Johns Hopkins campus. The study of living cells eventually led them to explorations of how cancer cells behave in different culture conditions. As Corner wrote, "Dr. and Mrs. Lewis led a quiet life of devotion to work in their laboratory. They were seldom seen apart. Their vacations were generally spent at Woods Hole, later at the Mt. Desert Island Biological Laboratory, where they varied their work by observations and experiments on marine organisms" (Corner 1967, 342).

Margaret Reed Lewis

Margaret Reed Lewis was born in Kittanning, Pennsylvania, in 1881. She received her BA degree from Goucher College, then studied at Bryn Mawr College, Columbia University, and abroad at Zurich, Paris, and Berlin, though she did not receive a graduate degree. Her studies included regeneration in amphibians and crayfish, and she served as an assistant to Thomas Hunt Morgan at both Bryn Mawr and Columbia. She taught as an assistant in zoology at Bryn Mawr in 1901–2 and at the New York Medical College for Women in physiology, and then served as a lecturer at Barnard College, and later trained nurses at Johns Hopkins. In 1910, she married Warren Lewis and began a long and fruitful career of collaboration in cell biology, embryology, and related studies. That work built on her 1908 visit to Berlin, where she transplanted guinea pig bone marrow into a solution of nutrients for culturing tissue in an experiment later cited as the first successful culture of mammalian cells. The Lewises went on to develop highly successful approaches to culturing tissues in different growth media and produced impressive videos of the process (Landecker 2004). In 1915, Lewis became a researcher at the Carnegie Institution of Washington Department of Embryology.

Frank Rattray Lillie

Frank Rattray Lillie was born in 1870 in Toronto, and was brother to Ralph Stayner Lillie. He received his BA from the University of Toronto, where he became intrigued by embryology. This led him to the MBL where Charles Otis Whitman recruited Lillie for studies of cell lineage in the freshwater mussel *Unio*. Whitman enticed Lillie to graduate study at Clark University in 1891 and then to the University of Chicago, where Whitman moved in 1892 to take up the first directorship of zoology. Lillie received his PhD degree two years later. At the MBL, Lillie became course instructor for the embryology course when it began in 1893. Lillie held positions at the University of Michigan and Vassar College, then returned to the University of Chicago as assistant professor of embryology and remained there throughout his career as professor, chairman of the Department of Zoology, and dean of the Division of Biological Sciences until he retired. He was a talented administrator, who helped shape and sustain both the University of Chicago and the MBL. His research included a textbook on *The Development of the Chick* in 1908, study of marine invertebrates, and study of freemartins in Chicago. His study of fertilization was regarded as his most important contribution, despite disagreements about interpretation. It is this work, developed in *Problems of Fertilization* in 1919 and updated in 1924 with his student Ernest Everett Just, that they present in the Cowdry volume. That work involved what Lillie referred to as "a working hypothesis" that a substance, "fertilizin," contributed to the joining of egg and sperm. Lillie continued to support his students, especially Just (Willier 1957).

Ernest Everett Just

Ernest Everett Just was born in 1883 in Charleston, South Carolina, and was sent to a boarding school, the Kimball Union Academy in Meriden, New Hampshire. He graduated from Dartmouth College in 1907 *magna cum laude* as a Rufus Choate scholar. He began teaching at Howard University in Washington, DC, and soon became chair of the zoology department. Just began going to the MBL in 1909, where he worked with Frank Lillie, studying the process of fertilization as the starting point for individual development. Just received his PhD from the University of Chicago for this work. It is not surprising that Lillie would invite Just to join him as coauthor on the chapter for the volume. Biographer Kenneth R. Manning has written a definitive and provocative interpretation of Just's scientific contributions and his place in the history of biological sciences as well as in the culture and life of academic society more generally (Manning 1983).

Edwin Grant Conklin

Edwin Grant Conklin had a large presence in cell biology and at the MBL, as seen in stories in an interview taped just days before his death (Conklin 1952). Conklin was born in 1863 in Waldo, Ohio. The family lived on a farm, and Conklin worked while attending a country school with one room and one teacher. He studied natural history at Ohio Wesleyan University and received his degree in 1885. While teaching at the missionary college for blacks, Rust University, from 1885 to 1888, he met and married Belle Adkinson. They had three children. Conklin received his PhD from Johns Hopkins in 1891. He studied embryology, cells, and related topics, while also working to reconcile his Methodist convictions with evolutionary biology. While at Johns Hopkins, William Keith Brooks sent Conklin and other students to the US Fish Commission station in Woods Hole. Very quickly, Conklin learned about the MBL just across the street, where he met Whitman and began his own cell lineage studies under Whitman's encouragement. His study of ascidian eggs became his dissertation work, and his completed work made up 226 pages, 9 plates, and 105 colored figures in the *Journal of Morphology*. Conklin enjoyed explaining how his dissertation very nearly bankrupted the journal. His work demonstrated how cells divide, step by step, and acquire differentiation in their different locations within the embryo. Conklin builds on that work in his essay in the Cowdry volume. At first Brooks had been skeptical of Conklin's proposal to study cell lineage, but in the end Brooks said, "Well, we give students degrees for counting words in classics, so I guess we can give you a degree for counting cells" (Harvey 1958).

Clarence E. McClung

Clarence E. McClung was born in 1870 in Clayton, California. He received a Bachelor's and PhD degree from the University of Kansas and then became professor and dean of the medical school there. In 1912, he went to the University of Pennsylvania as director of zoology and remained until he retired in 1940. He also chaired the Division of Biology and Agriculture of the National Research Council through World War I, serving from 1912 to 1921. After retiring, he spent one year at the University of Illinois as acting director of the Department of Zoology and then became the acting head of the Department of Biology at Swarthmore. His obituary in the *New York Times* reported that his one hundred or so students had honored his "profound influence on individuals and organizations concerned with biological research" (*New York Times* 1946). McClung's study of heredity led him to hypothesize that in grasshoppers, the number of X chromosomes determines the sex of an individual organism. Males lack a second X chromosome, which led to the idea of a sex-determining chromosome and provided early evidence that a particular chromosome carries a definable set of hereditary units and thereby shapes inheritance. His discussions of heredity stimulated others, such as Thomas Hunt Morgan.

Thomas Hunt Morgan

Thomas Hunt Morgan was born in 1866 in Lexington, Kentucky, into a family with deep roots in US history. Morgan received his BS degree from the University of Kentucky and his PhD from Johns Hopkins in 1891, following Wilson and along with Conklin. From Hopkins, Morgan followed Wilson to Bryn Mawr College, because Wilson had just left for Columbia. One of his students, Lilian V. Sampson, was especially notable, and he married her in 1904. They worked together on embryological research at Columbia and the MBL. In 1904, Morgan again followed Wilson to Columbia, where he remained until he left for Caltech in 1928. Morgan spent most summers at the MBL as a trustee and an active researcher. Morgan is best known for his work on fruit fly genetics, for which he received a Nobel Prize. Yet his work on regeneration of planarians, earthworms, and hydra, culminating in *Regeneration* in 1901, continues to play a role in stimulating how we interpret regeneration. Morgan studied many different species, and continued to do so even after achieving his reputation with flies (Sturtevant 1959; Allen 1978).

Initially, Cowdry's volume was to include an essay by Jacques Loeb on physical chemistry, with a special focus on proteins. Loeb was one of the luminaries of late nineteenth- and early twentieth-century biology. He asked challenging questions and posed provocative interpretations about the nature of life, and he supported a physicochemical interpretation of the mechanics of organisms. Loeb's work was always stimulating, and the contributors had surely benefited from Loeb's presence at the MBL over the years. Unfortunately, Loeb became ill and died in 1924 (Pauly 1987).

THE VOLUME

In his introduction to the volume, Wilson pointed to three periods of studying cells as he had with his own book, but in somewhat different terms. The first involved the early, largely structural, cell theory, while the second brought in modern cytology and embryology. The third involved Mendelian heredity, and therefore genetic analysis of cell phenomena and more study of the details of the cells. This period required bringing together cell morphology and physiology, biophysics and biochemistry, embryology, and genetics, and all together were leading to a new, "many-sided cellular biology" with increasing cooperation among approaches and among researchers (Cowdry 1924, 10). Wilson noted that "it is hardly possible to arrive at complete unity in a work produced by several collaborators representing widely diverse fields of research. Such a group, however, can at least bring to their task a broader and more critical knowledge of the subject than any single writer can at this day hope to command" (Cowdry 1924, 11). This commentary by the preeminent cell biologist set up the volume in a way that allowed each author considerable individual control over his topic.

Rather than providing a review of each chapter, it is useful to reflect on the approach of some of the chapters and the resulting whole. Many of the chapters seem rather surprising in modern terms. In discussing chemistry, Mathews entitles his first section "Chemistry and Psychism" and discusses the chemistry of "mentality" and vital forces as well as such mystifying ideas as the "psychology of hydrogen." He invokes Sir Oliver Lodge's etherions, and emphasizes the importance of providing an explanation for how the living is created from the nonliving. Despite the rather remarkable quirks in his eighty-page chapter, he also covers a lot of contemporary discussion of molecular chemistry, even if his chemistry colleagues would not have recognized some of it. Mathews did not have the most forward-looking view when he concluded his chapter by noting that little was known about the chemistry of genes and that existing knowledge therefore seemed to weigh against the gene theory. Mathews nonetheless showed that, while the biochemistry of cells might leave much open for question, it was essential for understanding cells.

In contrast, Jacobs's discussion of cell permeability explicitly acknowledged how little was known and yet how important it would be to know about the process of crossing cell membranes. Cells do not contain everything that they will ever need from the beginning, so they must have permeability. But how that permeability works and what controls the diffusion of materials across the membrane remained unknown.

Ralph Lillie asked about how cells react to their environments. Understanding their reactions requires knowing about both the stimuli and the responses. As Lillie's chapter explores possible chemical, mechanical, electrical, and other possible factors influencing reaction, it becomes clear that here, too, remained many open questions. Yet Lillie introduced the idea that cells do react and are not completely autonomous or insular. The ability of cells to react to stimuli from outside is what makes cell-cell interactions, as they were called later, actually work; it allows individual cells to work together as whole coordinated and organized organisms. Ralph Lillie's chapter really just points to the interactions, which became much more important in later decades.

The first four chapters, including Wilson's introduction, all raised many more questions than answers. Clearly, a community of researchers had come to recognize that cells are themselves complex and are also parts of complex systems, requiring diverse kinds of methods and questions to increase understanding.

In his seventy-page chapter, Chambers provided a much more definitive report on the results of microscopic techniques for establishing the physical structure of protoplasm. Chambers acknowledged that there was more to be learned about asters and other details of the cleavage process, but also that researchers had already learned an astonishing amount about both the cytoplasm and nucleus. Whereas Mathews, especially, had veered toward the theoretical and abstract, Chambers grounded his discussion in concrete observations. The same is largely true also of Cowdry's own seventy-page chapter on the cellular parts—mitochondria, Golgi apparatus, and chromidial substance. Thus, we see a diversity of methods and approaches as well as topics.

In their sixty-two-page chapter, Warren and Margaret Lewis introduced experimental approaches, looking at cells in tissue culture. As the acknowledged authorities on this topic, their work focused on laying out the technique and observing how cells behave as a result of being moved to artificial media. Theirs is the only chapter in the volume with photographic plates, which had become a standard way to demonstrate the results of tissue culture experiments. They discussed work with a number of different kinds of cells and concluded the chapter with a short section on cell death in culture. In brief, cells in culture eventually die, they reported, and they did not know why. In fact, it took several more decades before researchers began to sort out factors leading to the death of cells under normal conditions as well as in the artificial conditions of tissue culture.

Fertilization was a more familiar topic by the 1920s, and it is worth noting that Cowdry included Frank Lillie and Just rather than Loeb on the eighty-five-page chapter on the topic. Lillie and Just, on the one hand, and Loeb, on the other, had rather different interpretations of what happens at fertilization and of the extent to which the process is strictly mechanical and chemical-physical (as Loeb said) or involves a special substance called fertilizin (as Lillie maintained) (Pauly 1987; Manning 1983). While Loeb had worked for a number of years at the MBL, Lillie served as the second and long-term director of the MBL. It is therefore not surprising that Cowdry included Lillie's and Just's interpretation and did not discuss the controversies. Perhaps because the debates had continued for a number of years already, this chapter comes across as more specific and established than some of the others.

The same is true of Conklin's forty-eight-page chapter on cellular differentiation. Conklin was a leader in examining the cell lineage in several invertebrate organisms and then pursuing the causes and patterns of differentiation in each case. Differentiation takes cells from a more general to a more specialized state and constitutes development, Conklin explained. The process of differentiation occurs because of changes in both the nucleus and the cytoplasm. For Conklin in 1924, it was not the genes that drive development, however. He held a common view of those focused on cells and embryology that "the genes or Mendelian factors are undoubtedly located in the chromosomes, and they are sometimes regarded as the only differential factors of development, but if this were true these genes would of necessity have to undergo differential division and distribution to the cleavage cells, as Weismann maintained. Since this is not true, it must be that some of the differential factors of development lie outside of the nucleus, and if they are inherited, as most of these early differentiations are, they must lie in the cytoplasm" (Cowdry 1924, 601). That sounds misguided, or at least over-simplified, to us today, but it made sense at the time in the face of existing evidence.

Two chapters followed Conklin's and focused on the nucleus and its contents. McClung's seventy-nine pages on the chromosome theory of heredity and Morgan's forty-two pages on Mendelian heredity focused on the contents of the nucleus in germ cells. Look inside the cell for the driver of living processes, these approaches said. Chromosomes and chromatin carry heredity—somehow. McClung concluded that "the chromosome theory as it stands is logical, consistent, and generally applicable to both plants and animals. Admittedly incomplete, it yet stands as one of the highest achievements in biology and offers the most promising guide to further advances" (Cowdry 1924, 682). Morgan emphasized that even though the nucleus and hereditary genes might contribute to driving what happens in the cell, the cytoplasm remains essential as well. We need, Morgan suggested, more information about the "physiological processes that take place in the chromosomes and in the cytoplasm" (Cowdry 1924, 728). That ended the book.

Throughout, the authors noted the need for more information, more understanding, and more success in putting together a picture of the complex organism and its interacting parts. Cells are organic units, and they are in a real sense alive. But they are not the sole factor in making up living organisms and are also responsive to environmental conditions and to changing internal conditions. Most of the authors went on to further studies that expanded on their summary review approaches here, and some of the ideas here were left behind with time. Yet the overall picture is one of growing understanding of the need for multiple approaches, perspectives, and interpretations of cell structure, function, and interactions. Many questions remained, with many opportunities for further study, some of which are picked up in other chapters in this volume.

REACTIONS TO *GENERAL CYTOLOGY*

Overall, reviewers responded enthusiastically to the edited volume. They recognized the challenges of having thirteen authors with relatively short contributions on each topic (though they seem relatively long as chapters). And, as always with edited volumes, they liked some sections better than others. All acknowledged that the authors were all leaders in their respective fields. And several noted that the volume could not have been written by any one person alone. It took a group to provide what they all acknowledged as an authoritative, comprehensive, and overall very impressive laying out of the contemporary study of cells.

A review in the *Nation* began by noting that "the summer capital of biology in America is at Woods Hole, Massachusetts. A couple of years ago some dozen of the leaders of this scientific convent decided that there should be a new book about cells" (Thone 1925). Another review by Raoul M. May in the history of science journal, *ISIS*, reviewed Cowdry's volume and Wilson's third edition together. He concluded that "too much good cannot be said of these two great contributions to science. While, however, Wilson's book is a milestone, the combined studies of the American investigators which together form *General Cytology* are a stepping-stone. Wilson has mainly elaborated, as in the previous editions of his book, on questions concerning cellular morphology, while *General Cytology* includes a great deal which is physiological in nature. The two books together are a splendid *mise au point* of all that is known concerning that most fundamental of all living structures—the cell." Wilson's was a classic volume, marking the state of a field, while Cowdry's also pointed to new ideas and directions for future study (May 1925, 214). Another review by Arvilla Meek Taylor in the *Chicago Evening Post Literary Review* summarized the book and concluded with a call for more such collaborative projects, "for nothing will do more to advance the cause of science as a whole than such efforts as this" (University of Chicago Archives).

Other reviews offered similar views, though a number of them did find parts of Mathews's chapter on chemistry decidedly odd. Cytologist J. Brontë Gatenby provided a long and detailed review, in which he pointed out what he found missing or misleading in places, though he applauded the volume as a whole. He referred to Mathews's discussion of chemistry and psychism, in particular with regard to understanding how life emerges. It is worth reflecting on this point more closely, because Cowdry, as editor, had allowed this part to remain. The persistence of the views Mathews espoused shows that in 1924 biologists were not yet clear on how cells gain life, nor how they make up living organisms. Mathews wrote, "It is in fact the luminiferous ether which has made things alive, for ether is the storehouse of energy; it is itself nothing else than space and time; energy and time" (Cowdry 1924, 185). Today, Gatenby's response seems reserved in its critique: "It is impossible for a working cytologist adequately to comment on such passages. They may mean something to the metaphysician, but one cannot help feeling that Prof. Mathews' views on the relationship between cell lipins and cell proteins, or on the biochemistry of development, would have been more useful" (Gatenby 1925, 186).

A few critics went further, suggesting that Mathews's chapter ought not to have been included at all. Wilder B. Bancroft, writing a six-page review for the *Journal of Physical Chemistry* noted that the Mathews chapter was decidedly the weakest. After quoting passages related to psychism and the soul of atoms, Bancroft concluded that "this sort of speculative metaphysics may be justifiable in a popular article; but it should not have been allowed in a book like this" (Bancroft 1925, 107). Fortunately, all the reviewers seem to have agreed that the other chapters ranged from very useful to excellent.

Indeed! Yet what Mathews shows, alongside the collection of chapters, is the range of ideas about cells that were available in 1924. While researchers had learned a great deal, much remained to be learned. Cowdry's volume was, in fact, a stepping stone. And the steps forward lead to more study of areas that are only hinted at in the Cowdry volume but became increasingly important, such as cell-cell interaction, cell signaling, gene transcription and regulation, and so on, including the range of topics discussed in other essays in our volume.

Deeper understanding of the cells themselves, if not of their interactions, began to appear in the 1928 and 1932 editions of *Special Cytology* (of two and three volumes, respectively) that Cowdry edited. Here, too, Cowdry brought together a collection of authors. He explained that the purpose was to present in more detail knowledge about the different kinds of cells. "The book," he explained, "is to be regarded as supplementary to an earlier volume called *General Cytology*." There, the authors looked at "the fundamental principles of architecture and activity which cells possess in common" (Cowdry 1928, vii). *Special Cytology* looked instead at the characteristics of specialized cells. The thirty-seven chapters allowed room for a variety of types of cells as well as some of the methods used to study them.

Conclusion

This brings us back to the 1940 celebration of a century of cells in *The Cell and Protoplasm*. That 205-page volume included relatively short chapters by very distinguished researchers on cells, protoplasm, cell walls, chromosomes and genes, enzymes, molecular structure, plant hormones, vitamins, differentiation, physiology, viruses, microorganisms, techniques, and a chapter by Charles Kofoid on "Cells and Organisms."

While these researchers had acquired more knowledge about details by this 1940 symposium and volume, it is striking how many of the papers again include acknowledgements about how much remained to be learned. Conklin noted that "the mystery of mysteries is not the mechanism of evolution, but the evolution of the mechanism by which cells and protoplasm came to have the organization that has resulted in 'the promise and potency of all life.' This is the great problem which is sure to occupy increasingly the attention of biologists in the future" (Moulton 1940, 18). Richard Goldschmidt pointed to the need to get past thinking in terms of individual particulate genes and to focus instead on connections and chromosomes, even though this work may be harder and not fully understood yet. But the volume showed that "nothing is gained by hiding the head in the sand, or by erecting sign-boards 'Verboten' or by calling names" (Moulton 1940, 66). Other contributions pointed to the lack of completeness, or to remaining unaddressed questions. As in 1925, cytology in 1940 was still in its early stages.

In 1959 Jean Brachet and Alfred E. Mirsky edited *The Cell: Biochemistry, Physiology, and Morphology*, which grew to five large volumes and showed how much, and in what ways, the field had expanded. They recognized the tremendous recent advances in molecular biology and genetics, and the ways that understanding the complex interactions of morphological and physiological factors, grounded in biochemistry, had truly revolutionized the understanding of cells. It is clearly true that the knowledge available had expanded, and that the way researchers understood cells and their roles had changed.

By the 1960s, researchers began to discover the details of and reasons for cell cycles, finding that cells go through predictable stages following molecular triggers. Lee Hartwell, Paul Nurse, and Timothy Hunt are credited with having observed that cycles occur and having worked to understand underlying mechanisms. They shared the 2001 Nobel Prize in Physiology or Medicine for their respective contributions, and the study of cyclin and cell cycles became a core way to interpret cell division (Nobel Prize 2001). Along with a growing understanding of cell death, the cell cycle work helped reinforce the idea of a cell that is itself alive, matures and specializes, and then dies.

Many other contributions added to our understanding of how each cell works, how they interact, and how that interaction makes up a whole organism that changes and responds to its environment. The regulation of that process, its timing, and the factors that influence it all come from the environment of other neighboring cells as well as from within the individual cell itself. Cells behave in part in response to their neighbors. They are therefore living units themselves, yes, and also parts of larger, whole, integrated complex systems. Finally, we have moved closer to integrating the different ideas about the roles of cells that Cowdry's group and others were trying to grasp. Yet, as those researchers all noted, there remains much more to be learned.

Acknowledgments
Thanks to the National Science Foundation, Arizona State University, and the Webster Foundation for generous and timely support, and to Karl Matlin, Richard Creath, and Kate MacCord for valuable suggestions.

References

Allen, Garland E. 1978. Thomas Hunt Morgan, the Man and His Science. Princeton, NJ: Princeton University Press.

Baer, Karl Ernst von. 1834. "Die Metamorphose des Eies der Batrachier vor der Erscheinung des Embryo und Folgerungen aus ihr für die Theorie der Erzeugung." *Müller's Archiv für Anatomie, Physiologie, und wissenschaftliche Medizin*, 481–509.

Baker, John Randal. 1948. "The Cell-Theory: A Restatement, History, and Critique–Part I." *Quarterly Review of Microscopical Science* , series 3, 89 (1): 103–25. (All parts are reprinted in Baker 1988.)

———. 1988. *The Cell-Theory: A Restatement, History, and Critique*. New York: Garland Publishing.

Bancroft, Wilder B. 1925. "Review of *General Cytology*." *Journal of Physical Chemistry* 29 (1): 106–11.

Billings, Susan M. 1971. "Concepts of Nerve Fiber Development, 1839–1930." *Journal of the History of Biology* 4: 275–305.

Bracegirdle, Brian. 1978. *A History of Microscopical Technique*. Ithaca, NY: Cornell University Press.

Conklin, Edwin Grant. 1952. "Reminiscences of Dr. Edwin Grant Conklin (1863–1952), Biologist." Parts 1 and 2. Deposited in the American Philosophical Society Archives. Available online at http://history.archives.mbl.edu/archives/formats/audio.

Corner, George W. 1967. "Warren Harmon Lewis, 1870–1964." In *Biographical Memoirs*, 323–58. National Academy of Sciences. Washington, DC: National Academies Press.

Cowdry, Edmund V., ed. 1924. *General Cytology: A Textbook of Cellular Structure and Function for Students of Biology and Medicine*. Chicago: University of Chicago Press.

———. ed. 1928. *Special Cytology*. New York: Paul B. Hoeber; 2nd ed., Chicago: University of Chicago Press, 1932.

Gatenby, J. Brontë. 1925. "*General Cytology*: A Textbook of Cellular Structure and Function for Students of Biology and Medicine." *Nature* 115 (2884): 185–87.

Goldring, Irene P. 1979. "Robert Chambers, 1881–1957." *American Zoologist* 19: 1271–73.

Harris, Henry. 1999. *The Birth of the Cell*. New Haven, CT: Yale University Press.

Harvey, E. Newton. 1956."Merkel Henry Jacobs and the Study of Cell Permeability." *Journal of Cellular and Comparative Physiology* 47: 5–10.

———. 1958a."Albert Prescott Mathews, Biochemist." *Science* 127: 743–744.

———. 1958b. "Edwin Grant Conklin, 1863–1952." In *Biographical Memoirs*, 54–91. National Academy of Sciences. Washington, DC: National Academies Press.

Hughes, Arthur. 1959. *A History of Cytology*. London: Abelard-Shuman.

Huxley, T. H. 1853. "The Cell-Theory." *British Foreign Medico-Chirurgical Review* 12: 285–314.

Landecker, Hannah. 2004. "The Lewis Films: Tissue Culture and 'Living Anatomy,' 1919–1940." In Jane Maienschein, Marie Glitz, and Garland Allan, eds., *Centennial History of the Carnegie Institute Department of Embryology*, 117–44. Cambridge, MA: Cambridge University Press.

Laubichler, Manfred D., and Eric H. Davidson. 2008."Boveri's Long Experiment: Sea Urchin Merogones and the Establishment of the Role of Nuclear Chromosomes in Development." *Developmental Biology* 314 (1): 1–11.

Lillie, Frank R. *Problems of Fertilization*. 1919. Chicago: University of Chicago Press.

———. 1908. *The Development of the Chick: An Introduction to Embryology*. New York: Henry Holt.

Lillie, Ralph S. 1945. *General Biology and Philosophy of Organism*. Chicago: University of Chicago Press.

———. Various papers. Ralph S. Lillie Papers. University of Chicago Archives. Online at https://www.lib.uchicago.edu/e/scrc/findingaids/view.php?eadid=ICU.SPCL.CRMS58).

Love, Warner E. 1971. "Markel Henry Jacobs" in the report for 1970. *Biological Bulletin*. 141(1): 15–17.

Maienschein, Jane. 1983. "Experimental Biology in Transition: Harrison's Embryology, 1895–1910." *Studies in History of Biology* 6:107–27

———. 1991. *Transforming Traditions in American Biology, 1880–1915*. Baltimore, MD: Johns Hopkins University Press.

———. 2011. "'Organization' as Setting Boundaries of Individual Development." *Biological Theory* 6 (1): 73–79.

———. 2014. *Embryos Under the Microscope: Diverging Meanings of Life*. Cambridge, MA: Harvard University Press.

Manning, Kenneth R. 1983. *Black Apollo of Science: The Life of Ernest Everett Just*. New York: Oxford University Press.

May, Raoul M. 1926. "Book Review: *General Cytology*, E. V. Cowdry; *The Cell in Development and Heredity*, Edmund B. Wilson." *Isis* 8 (1): 213–15.

Morgan, Thomas Hunt. 1940. "Edmund Beecher Wilson, 1856–1939." In *Biographical Memoirs*, 315–42. National Academy of Sciences. Washington, DC: National Academies Press.

Moulton, Forest Ray, ed. 1940. *The Cell and Protoplasm*. Washington, DC: American Association for the Advancement of Science, The Science Press.

New York Times. 1946. Obituary for Clarence E. McClung, January 19.

Nobel Prize. 2001. "The Nobel Prize in Physiology or Medicine." Online at http://www.nobelprize.org/nobel_prizes/medicine/laureates/2001/.

Park, Hyung Wook. 2008. "Edmund Vincent Cowdry and the Making of Gerontology as a Multidisciplinary Scientific Field in the United States." *Journal of the History of Biology* 41: 529–72.

———. 2016. *Old Age, New Science: Gerontologists and Their Biosocial Visions, 1900–1960*. Pittsburgh, PA: University of Pittsburgh Press.

Pauly, Philip J. 1987. *Controlling Life: Jacques Loeb and the Engineering Ideal in Biology*. New York: Oxford University Press.

Raspail, François-Vincent. 1833. *Nouveau système de chimie organique, fondé sue des methodes nouvelles d'observation*. Paris: Ballière. Quoted in Harris 1999, 32.

Richmond, Marsha. 2002. "Thomas Henry Huxley's Developmental View of the Cell." *Nature Reviews Molecular Cell Biology* 3: 61–65.

Schwann, Theodor. 1839. Published in English as Schwann, Theodor. 1847. *Microscopical Researches into the Accordance in the Structure and Growth of Animals and Plants*. Translated by Henry Smith. London: Printed for the Sydenham Society. Available

online at http://www.biodiversitylibrary.org/ia/microscopicalres47schw#page/9/mode/1up.
Sedgwick, Adam. 1894. "On the Inadequacy of the Cellular Theory of Development, and on the Early Development of Nerves, Particularly of the Third Nerve and of the Sympathetic in Elasmobranchii," *Quarterly Journal of Microscopical Science*, series 2, 37 (145): 87–112.
Sharp, Lester W. 1943. *Fundamentals of Cytology*. New York, McGraw-Hill.
Sturtevant, A. H. 1959. "Thomas Hunt Morgan, 1866–1945." In *Biographical Memoirs*, 283–325. National Academy of Sciences. Washington, DC: National Academies Press.
Thone, Frank. 1925. "A Monument in Biology." *Nation*, April 1, 361.
University of Chicago Archives, Special Collections of the University of Chicago Library, box 127, folder 1. Thanks to Karl Matlin for finding and sharing this information.
Whitman, Charles Otis. 1893. "The Inadequacy of the Cell-Theory of Development," *Journal of Morphology* 8: 639–58.
Willier, B. H. 1957. "Frank Rattray Lillie, 1870–1947." *Biographical Memoirs*, 179–236. National Academy of Sciences. Washington, DC: National Academies Press.
Wilson, E. B. 1895. *An Atlas of Fertilization and Karyokinesis of the Ovum*. New York: Macmillan. Available online at http://www.biodiversitylibrary.org/bibliography/6244#/summary.
———. 1896. *The Cell in Development and Inheritance*. New York: Macmillan.
———. 1925. *The Cell in Development and Heredity*. 3rd ed. New York: Macmillan. Orig. pub. as *The Cell in Development and Inheritance* in 1896; 2nd ed., 1900.