Visions of Life and Matter:
Protoplasm, Scientific Microscopy, and the Origins of Molecular Biology, 1839–1941

by
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To Melissa, Molly, Nick, Stephen, and Vicki – my history of science family.

Abstract

For a century, anyone with sympathies towards materialism and reductionism in biology could say that most important stuff in a living organism was *protoplasm*, often referred to as "living matter" and the "physical basis of life." By examining the confluence of biology's material and visual cultures of the cell, this dissertation seeks to open the "black box" of the physico-chemical, materialist conception of life as protoplasm. The dissertation argues that the material and ontological foundations of biology changed twice during the century of protoplasm, from the 1840s to the 1930s. The first major change began in 1899, when protoplasm became defined as a colloid — a heterogeneous aggregate whose structure and behavior came from a delicate balance of thermodynamic interactions of their material phases, rather than an assembly of individual molecules. Through colloid chemistry biologists became suspicious of arguments about definite molecular structures in the soft, vital parts of living organisms — and not just because of colloid chemistry's associations with nominalist, energy-centric physics. By the end of the nineteenth century, many biologists had become skeptical of the chemical fixation techniques needed to see sub-cellular structures, and ordinary light microscopes had reached the limits of their theoretical resolving power. The second major change to protoplasm theory came to a head in the 1930s, as biologists sought to use indirect techniques to overcome microscopy's resolution limits, and to visually disaggregate colloids into their component parts. Crucially, these techniques required extensive use of diagrams and schematic illustrations to make visible a "biological microworld" of the molecular "ultrastructure" of cells, both in the imagination and on paper. The second half of the dissertation examines three pioneers in cell ultrastructure research, and their use of polarized light microscopy to create this biological microworld: Herman Ambronn, Albert Frey-Wyssling, and Wilhelm J. Schmidt. By investigating how biologists developed their own theories of living matter, this dissertation shows that they engaged with physics and physical chemistry decades before the post-war biophysics boom, and offers a new history of how biologists began to imagine and explore life at the molecular level.

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Both my dissertation and I are products of the phenomenal intellectual and scholarly environments we have had the privilege of inhabiting for the last seven years. It is my firm belief that this work and my own way of thinking have been shaped by the tremendous support I have received from the faculty and my fellow graduate students at the University of Wisconsin-Madison's Program in the History of Science, Medicine, and Technology. My sincerest thanks to are due to my committee members, Catherine Jackson, Nicole Nelson, and Florence Hsia, for your patience, care, and thoughtful comments on what was/is at times a difficult piece to get through. Nicole and Florence have also been supportive as my mentors and career advisors, for making me into a skilled and dedicated teacher, and for being a consistent and much needed source of levity and silliness in my life — I am sorry I will never get to teach for you again, nor wear a bright pink sash that invites compliments from complete strangers. One of the many beating hearts of this dissertation would not have come alive without the efforts of Richard Staley, who provided my entire education in the history and philosophy of the physical sciences, and who, in his unique way, demonstrated descriptivist positivism to me before I ever comprehended it.

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On a very practical level, this dissertation could only have been written with the advent of full text searches of historical materials through digital library repositories; keyword searches are the only way I could have managed to write about such a large swath of history, focused on a few specific ideas and concepts. My research owes a great deal to the continued work of the Biodiversity Heritage Library, Hathi Trust, Medical Heritage Library, Google Books, the Internet Archive, and Zotero. I hope this dissertation stands as a testament to what these kinds of digital methods can do, as well as a reminder that digital full text and keyword searches must be used with careful consideration of historical context and research.

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Table of Contents

Abstract ..... ***ii***

Acknowledgements ..... ***iii***

Introduction: Living Matter **1**
a. Visual and material cultures of protoplasm 4
b. Chapter outline 12
c. Molecules, biophysics, and the historiography of "molecular biology" 15

Chapter 1: The "Cell" and "Protoplasm" as Container, Object and Substance **25**
a. Schleiden, Schwann, and the mechanics of cell growth 30
b. Hugo von Mohl's Primordialschlauch 36
c. Sarcode and protoplasm 45
d. Conclusion: protoplasm as the "Physical Basis of Life" 54

Chapter 2: The Structure of Protoplasm and Fixation Artifacts, 1882–1899 ..... **59**
a. Osmic acid, protoplasmic frameworks, and Flemming's fibrillar theory 64
b. Artifice and the coagulating protoplasm 68
c. Alfred Fischer's catalog of fixation artifacts 72
d. William Bate Hardy and the colloidal structure of protoplasm 81
e. Conclusion 85

Chapter 3: *Protoplasmatologia* and the "Dark Age of Biocolloidology," 1899–1930 ..... **87**
a. Positivism and the history of colloid chemistry 92
b. Protoplasm studies in the early twentieth century 100
c. The historiography of biochemistry and the "Dark Age of Biocolloidology" 111

Chapter 4: Crystals, Colloids, and Fibers **117**
a. Nägeli's "molecules" and the micelle 124
b. Hermann Ambronn in the micellar wilderness 133
c. Colloids, scientific microscopy, and the Wiener Mischkörper 140
d. Albert Frey-Wyssling, cell wall structure, and the "principle of repetition" 154
e. Conclusion: polarized light microscopy and early electron microscopy 164

Chapter 5: The Building Blocks of the Biological Microworld, 1924–1941 ..... **171**
a. W. J. Schmidt and the "Bausteine" *of animal bodies* 176
b. The "molecule" up to 1924 182
c. Interpreting surface tension: molecular orientation 187
d. Colloid chemistry and the iconography of molecular orientation 192
e. Lipids, fiber chains, and the molecular biological microworld 198
f. Conclusion 203

Conclusion: Molecular Biology and the End of Protoplasm **207**

Appendix: Birefringence, Polarized Light, and Polarized Light Microscopy **215**

Bibliography **218**

Figures **241**

Introduction: Living Matter

> My own scientific career was a descent from higher to lower dimension, led by the desire to understand life. I went from animals to cells, from cells to bacteria, from bacteria to molecules, from molecules to electrons. The story had its irony, for molecules and electrons have no life at all. On my way life ran out between my fingers.
>
> —Albert Szent-Györgyi, *The Living State*, 1972[1]

On May 26, 1939, at a celebration of the centenary of Matthias Schleiden and Theodor Schwann's cell theory, the German biologist Wilhelm Josef Schmidt (1884–1974) declared that the future of cell research lay in "the organization of the cell's molecular order."[2] At this lecture, titled "*Der molekulare Bau der Zelle*," Schmidt presented the first ever schematic image of the cell protoplasm rendered in full molecular detail (Figure A): an image with individual lipid molecules forming vacuoles and liposomes, triglyceride molecules forming a huge droplet of fat, individual molecules of water drawn as tiny circles, and centipede-like protein chain molecules running all throughout, forming the delicate cytoskeleton that held the whole cell together. The image was not an illustration of any particular thing that Schmidt had seen: it was an argument that biologists needed to change the way they thought about matter and the materials that made up living organisms. This diagram was Schmidt's answer to why, for a century, the protoplasm had stubbornly refused to reveal any structure when viewed under the microscope, even with the newest modern techniques in slit ultra-microscopy and polarized light microscopy. "The tangled position of the molecules negates the optical anisotropy of a single molecule, by forming the same *mean* refractive

1. Albert Szent-Györgyi, *The Living State, with Observations on Cancer* (New York: Academic Press, 1972), 7.
2. W. J. Schmidt, "Der molekulare Bau der Zelle," *Nova Acta Leopoldina* 7 (1939): 1–24, on 7.

All emphases in this dissertation are original to their source, unless otherwise indicated. All translations are my own, unless a translation is cited. The original German terminology will occasionally be indicated in the text, in italics.

index for all directions," Schmidt explained — a negation that made the protoplasm transparent, almost clear. "Since protoplasm usually shows *no birefringence*, the protein molecules must run wild, in all directions, forming a uniformly constructed *framework*." ("*Da nun Protoplasma für gewöhnlich* keine Doppelbrechung zeigt*, so müssen die Proteinmolekeln wirr verlaufen, ein nach allen Richtungen gleichmäßig ausgebildetes* Gerüstwerk *bilden.*")[3]

Schmidt's argument, built explicitly on an *absence* of visual testimony, could only have been made by a biologist who was fully convinced that a microworld of atoms and molecules formed the material foundation of biology — and his image of the molecular structure of the protoplasm was, in turn, meant to convince everyone else of this new molecular metaphysics.[4] This was not just a synthesis of decades of biophysical and physico-chemical research or theory: this was a world view, a *Weltbild* that drew from the molecular imagery that had been proliferating across the physical and biological sciences in the 1930s. Before this, biologists' drawings of cellular structures were largely representations of what could be seen under the microscope, and even these structures could be made visible only through the application of fixative chemicals and dyes to dead, prepared tissues. A scientific image of the cell like Schmidt's would have been unimaginable in the 1920s, no matter how schematic, and such images were nearly nonexistent. Schmidt's image shows us historically that biological reasoning at the histological, cellular, and sub-cellular levels — at least the kinds that tended towards materialism and reductionism — had by 1939 become molecular.

This dissertation is in large part the long history of Schmidt's image, both as a historically specific scientific-cultural event and as a display of technical prowess: how it came to be, what it meant, the people who played a role in its creation, why it appeared when it did, and why it could

3. *ibid.,* 12, 15–16.

4. Unless specific disciplinary differences need to be noted, this dissertation will use the term "biology" to include what was meant by "physiology" in the nineteenth- and early twentieth-centuries, along with "biologist" and "physiologist."

not have appeared much earlier. It is an historical study of both the visual and the material culture of the biological microworld, and an examination of what biologists thought living cells were made of. It is also a history of microscopy within late nineteenth and early twentieth century biology: biologists' epistemological assumptions about the powers and limits of microscopic vision were intimately linked to their notions of what living matter was. This dissertation will argue that there were not one, but *two* major changes to biologists' ontologies and approaches to matter in the first century of cell theory. In the nineteenth century protoplasm was a substance whose material qualities were loosely defined as "glutinous," or "transparent," or some mixture of carbon, nitrogen, oxygen, and phosphorus in an as-yet-undetermined proportions. The first major change to the ontology of life happened in 1899 when protoplasm became defined as a colloid — a heterogeneous aggregate whose structure and behaviors were thought to come from a delicate balance of energetic and thermodynamic interactions of their various material phases, rather than a specific assembly of individual molecules. To colloid chemists, following kinetic and thermodynamic theories from the late nineteenth-century, molecules were less relevant, less visible, less real entities, compared to the scientific certainty of precise, instrumental measurement of temperature, movement, viscosity, or surface energy of the continuous colloidal system. It was no accident that in the heyday of colloid biology the dominant visual idiom was the graph, familiar from physiology, plotting changes in measurable physical variables in protoplasm over time. Then, beginning in the 1930s, life and protoplasm were molecularized, in a fashion familiar to us today: individual molecules gained agency and relevance, discontinuity between molecules was emphasized, microphysical reasoning reasserted itself, and visual representations of the biological microworld began to proliferate in journals, textbooks, and classrooms. These changes in theories of protoplasmic structure and ideas of living matter occurred in a variety of different scientific contexts, and each of the following chapters will pay close attention how different kinds of scientific questions, experimental systems, and ideas of

matter shaped each scene of inquiry.[5] In the fast-moving decade before Schmidt's molecular diagram of the protoplasm, biologists were rapidly changing their conceptions of what living matter *is*, and their habits for how to think about and represent living matter on paper.

a. Visual and material cultures of protoplasm

That the microworld exists in the visual and material worlds simultaneously, and that the microworld exists only through a combination of visualization and material practice, is not an entirely new revelation, though it has been emphasized in the history and philosophy of science only in the last fifteen years. This latest scholarship has shown that the microworld of atoms and molecules can only become real to scientists if they possess legitimate ways of manipulating those invisible particles. When the object being practically manipulated in the laboratory is at the scale of a cell, an organism, or an Erlenmeyer flask, visualizing, imagining, diagramming, and modeling become indispensable scientific activities for resolving those familiar objects at the scale of atoms and molecules.[6] Just because molecules are invisible to the eye does not mean molecules cannot be visible to the mind's eye.[7]

The move towards examining how scientific visual culture constitutes the material world is most notable in the historiography of the physical sciences, where past debates over ontology and the

5. Nicholas Jardine, *The Scenes of Inquiry: On the Reality of Questions in the Sciences* (Oxford: Clarendon Press, 1991). "The questions real in a [scientific] community are identified as those which they can see how, in principle, to 'get to grips with' — a little more explicitly, they are the questions for which there exist considerations that would be acknowledged in the community as providing *grounds for preferring one full and direct answer over all the others*."

6. Jed Buchwald was one of the earliest historians of physics who argued that the microworld only becomes "pragmatically real" when it can be manipulated, and in modern physics he dates this to only after ca. 1893. See Jed Z. Buchwald, "How the Ether Spawned the Microworld," in *Biographies of Scientific Objects*, ed. Lorraine Daston (Chicago: University of Chicago Press, 2000), 203–25, on 215 and 221.

7. M. Norton Wise, "Making Visible," *Isis* 97, no. 1 (March 2006): 75–82.

continuity or atomicity of matter have been fundamental for historians and scientists alike.[8] Alan Rocke and Ursula Klein have shown that the use of mental imagery and the manipulation of semiotic signs on paper were crucial epistemological steps towards making chemical molecules more real to organic chemists in the nineteenth century.[9] Likewise David Kaiser has argued that Feynman diagrams used in particle physics, while formally only tools for keeping track of complicated mathematical operations, became a quasi-visual way of intuiting how subatomic particles interact in quantum field theory. Kaiser also shows that Feynman diagrams were one of the few, rapid ways of sharing and teaching particular forms of intuition in theoretical physics.[10] Charlotte Bigg has shown how Jean Perrin in 1909 used simplified drawings of Brownian motion to argue for the existence of atoms and molecules, despite the fact that he still could not see them (Figure B). Perrin, Bigg argues, used a rhetoric of controlled, precise observation and measurement, while also presenting a diagram that depicted Brownian motion in a simplified, statistically averaged, flattened form: the idealized schematic of the "random walk" made more intuitive and mathematical sense than a photograph. A hand-drawn diagram proved to be a more precise, if less "objective" proof than photographs for the existence of a molecular reality.[11] An early exemplar of this visual-material approach in the history of biology is Cambrosio, Jacobi, and Keating's study of Paul Ehrlich's sea-creature-like images from the 1910s and '20s of molecular, antibody "side-chains" (Figure C): these odd molecular images resemble

8. Everett Mendelsohn, "The Continuous and the Discrete in the History of Science," in *Constancy and Change in Human Development*, ed. Orville G. Brim, Jr. and Jerome Kagan (Cambridge: Harvard University Press, 1980), 75–112.

9. Alan J. Rocke, *Image and Reality: Kekulé, Kopp, and the Scientific Imagination* (Chicago: University of Chicago Press, 2010); Ursula Klein, ed., *Tools and Modes of Representation in the Laboratory Sciences*, Boston Studies in the Philosophy of Science, vol. 222 (Dordrecht: Kluwer, 2001); Ursula Klein, *Experiments, Models, Paper Tools: Cultures of Organic Chemistry in the Nineteenth Century* (Stanford: Stanford University Press, 2003).

10. David Kaiser, *Drawing Theories Apart: The Dispersion of Feynman Diagrams in Postwar Physics* (Chicago: University of Chicago Press, 2005). On visual culture and pedagogy in the life sciences, see Nancy Anderson and Michael R. Dietrich, eds., *The Educated Eye: Visual Culture and Pedagogy in the Life Sciences* (Hanover: Dartmouth College Press, 2012).

11. Charlotte Bigg, "Evident Atoms: Visuality in Jean Perrin's Brownian Motion Research," *Studies in History and Philosophy of Science Part A* 39, no. 3 (September 2008): 312–22; and, "A Visual History of Jean Perrin's Brownian Motion Curves," in *Histories of Scientific Observation*, ed. Lorraine Daston and Elizabeth Lunbeck (Chicago: University of Chicago Press, 2011), 156–79.

post-WWII "lock-and-key" images, but Cambrosio, Jacobi, and Keating show that these images were widely disdained or dismissed as merely heuristic or mnemonic, with little empirical basis.[12] Most visual-cultural explorations of molecules in biology are, unsurprisingly, histories of the DNA double helix and its aftermaths. For example, Soraya de Chadarevian has explored how Watson and Crick built their first model of the double helix out of metal and clamps and the role the model played in disseminating their theory, while Angela Creager and Gregory Morgan have shown how Rosalind Franklin and the other crystallographers argued over theories of virus structure by drawing molecular models and fitting together protein and nucleic acid building blocks on paper.[13] Most recently the anthropologist Natasha Myers has studied the material culture of contemporary protein crystallography, and how intuition and "expert sensoria" (the coordination of "the body's perceptual and proprioceptive" capacities) constitute crystallographers' ability to translate x-ray diffraction diagrams into three-dimensional, dynamic protein models.[14]

This dissertation approaches the visual and material cultures of biology by examining the relationship between scientific microscopy and theories of matter, and the relationship between techniques of vision/magnification and assumptions about reality. The approach that this dissertation takes to the visual and material cultures of biology hews much more closely to Bigg's study of Perrin Brownian motion diagrams than it does to the literature in the history of (molecular) biology: the issues and historical debates examined here are *not* about modeling, heuristics, or intuitions, though all three will appear in the following chapters. Rather, this dissertation will show how biologists argued about the nature of matter itself, often by way of arguing about the legitimacy of different

12. Alberto Cambrosio, Daniel Jacobi, and Peter Keating, "Ehrlich's 'Beautiful Pictures' and the Controversial Beginnings of Immunological Imagery," *Isis* 84, no. 4 (December 1993): 662–99.

13. Soraya de Chadarevian, *Designs for Life: Molecular Biology After World War II* (Cambridge: Cambridge University Press, 2002), esp. ch. 5, on the physical double-helix model and "televisual language"; and Angela N. H. Creager and Gregory J. Morgan, "After the Double Helix," *Isis* 99, no. 2 (June 2008): 239–72. See also Soraya de Chadarevian and Nick Hopwood, eds., *Models: The Third Dimension of Science* (Stanford: Stanford University Press, 2004).

14. Natasha Myers, *Rendering Life Molecular* (Durham: Duke University Press, 2015), see 20–22.

kinds of microscopic technique. In this dissertation, paper diagrams, imaginative faculties, and what could be seen in the mind's eye were all aids to microscopy: biologists' debates about the nature of microscopy and of microscopic vision in turn affected the way biologists understood and studied living matter.

Despite its immediate, almost visceral clarity, beauty, and meaningfulness to a viewer today, in 1939 Schmidt would have known that his conceptual diagram of the molecular structure of protoplasm would have been a revelation to a sizable part of the audience gathered before him. Schmidt's ability to see such molecular-structural specificity in protoplasm ran counter to many of the explicitly non-visual theories and intuitions about matter that biologists had cultivated since the turn of the century. For nearly three decades, the consensus among biologists was that the cell and protoplasm had no obvious molecular structure, and that protoplasm was a colloidal, slimy, and heterogeneous aggregate. Protoplasm was often described as "translucent," "viscous," "clear," and "hyaline." The idea that cells and protoplasm were colloidal made immediate visual and tactile sense, it was confirmed by strong experimental evidence, and it fit into a larger conceptual and theoretical universe — a conceptual and theoretical universe that believed molecules were just invisible particles, that they were probably spheres, and that they could not account for either biological structure or the phenomena of life.

What ultimately allowed Schmidt to create his molecular diagram of the protoplasm was that biologists' ideas of matter changed. Starting from the origins and controversies of the cell theory in the 1840s and ending with Schmidt's image of the protoplasm in 1939, this dissertation will explore how biologists' conceptions and approaches towards *life* changed as their ideas and attitudes towards *matter* changed. To paraphrase Jed Buchwald, the shape and texture of much contemporary life

science depends directly on the vivid presence of the biological microworld.[15] Hence this dissertation's argument that our current conception of the biological microworld became real to most biologists only in the 1930s, after the second of the two major transformations to the ontological foundations of modern biology — the first time when Schmidt's molecular diagram of protoplasm was possible, and the only period in which it was an argument and not just a picture, a theory whose case Schmidt needed to plead in 1939, rather than a mere matter of fact.

This dissertation will also argue that biologists explored the nature of matter through their explorations of protoplasm, and that research on protoplasm was a major avenue through which biologists explored the rapidly changing landscape of the physical sciences. The term "protoplasm" became synonymous with the phrases "living matter," "living substance," "the physical basis of life," or "*lebende Substanz*" in the 1860s; Chapter 1 will show how "protoplasm" transformed from a term of art in botany, indicating the contractile and generative part of the plant cell, into a unifying material theory of life. The phrase "living matter" was so pervasive that in 1969, the biologist Thomas S. Hall (1909–1990) thought it sensible to write a two-volume history of the "life-matter problem," from Ancient Greece to 1900.[16] Although a phrase like "living matter" would be suspect if uttered today, for most of a century this was a way for a biologist to demonstrate their materialist sensibilities, and to indicate that they were not the kind of biologist who was prone to invocations of vital forces.[17]

The identity of protoplasm with life itself was such a well established convention that the 1911 *Encyclopedia Britannica* entry for "Life" began simply with a direct, slightly condescending

15. Jed Z. Buchwald, "How the Ether Spawned the Microworld," 215.

16. Thomas S. Hall, *Ideas of Life and Matter: Studies in the History of General Physiology, 600 B.C.-1900 A.D.* (Chicago: University of Chicago Press, 1969).

17. Gerald L. Geison, "The Protoplasmic Theory of Life and the Vitalist-Mechanist Debate," *Isis* 60, no. 3 (October, 1969): 273–92.

declaration: "Life, the popular name for the activity peculiar to protoplasm *(q.v.)*." It went on to explain that,

> This conception has been extended by analogy to phenomena different in kind, such as the activity of masses of water or of air, or of machinery, or by another analogy, to the duration of a composite structure, and by imagination to real or supposed phenomena such as the manifestations of incorporeal entities. From the point of view of exact science life is associated with matter, is displayed only by living bodies, by all living bodies, and is what distinguishes living bodies from bodies that are not alive. Herbert Spencer's formula that life is "the continuous adjustment of internal relations to external relations" was the result of a profound and subtle analysis, but omits the fundamental consideration that we know life only as a quality of and in association with living matter.[18]

Life, as defined and studied by scientists, was an activity, one exclusively found in the *protoplasm*, "living matter," the so-called "physical basis of life." The historian Robert Brain has argued that this definition, written by the zoologist Peter Chalmers Mitchell, reflected the importance of the protoplasm concept to the development of nineteenth century physiology: the idea that life was a kind of matter in motion imbued with vitality led scientists, philosophers, and artists alike to try to capture and interpret its manifold pulsations, movements, and vibrations.[19] Late nineteenth-century physiologists and physiological enthusiasts believed, Brain argues, that any activity of animal, plant, human, psychic or spiritual life — anything from respiration to thought, to the capacity for speech or the appreciation of beauty — could be understood by studying protoplasm, and vice versa.[20]

Mitchell insisted, however, that the consideration of living matter was just as fundamental as considering its activity — its active self-adjustment and adaptation to the environment — if not more so. If protoplasm was, as per T. H. Huxley's formulation in 1868, the "physical basis, or matter of life," then what was that matter, and what was the nature of that matter?[21] As late as 1817 Georges Cuvier could claim that such a question was one with which biologists need not concern themselves.

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18. Peter Chalmers Mitchell, "Life," *Encyclopedia Britannica*, 1911.

19. Robert Brain, *The Pulse of Modernism: Physiological Aesthetics in Fin-de-Siècle Europe* (Seattle: University of Washington Press, 2015).

20. In this way the broad cultural, scientific, and technological importance of the protoplasm was similar to that of the luminiferous ether; see Iwan Rhys Morus, *When Physics Became King* (Chicago: University of Chicago Press, 2005).

21. T. H. Huxley, "On the Physical Basis of Life," *The Fortnightly Review*, n.s., 5 (1869): 129–45, on 129.

Implicitly invoking René Descartes' theory of corpuscular vortices, Cuvier wrote that, "Life is a vortex, more or less rapid, more or less complicated, the direction of which is constant, and which always carries along molecules of the same kind, but into which individual molecules are continually entering, and from which they are constantly departing." The molecules themselves were inaccessible, unintelligible, and inconsequential: only the vortices, *i.e.* the forms of the motions of the molecules, were relevant to biologists. "The *form* of a living body," wrote Cuvier, "is more essential to it than its *matter*."[22]

The history of biology is largely a history of the sciences that study the manifold forms of living organisms, the vital phenomena that those organisms exhibit, and the environments living organisms inhabit.[23] Philosophers and historians of biology have, with good reason, focused on the *living* half of the phrase "living matter": life has, after all, been the fundamental topic of biology, and the idea still packs a rhetorical punch in critical science studies.[24] Yet, during the age of protoplasm,

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22. Georges Cuvier, *Le règne animal distribué d'après son organisation: tome I, contenant l'introduction, les mammifères et les oiseaux* (Paris: Chez Déterville, 1817), 13. "La vie est donc un tourbillon plus ou moins rapide, plus ou moins compliqué, dont la direction est constante, et qui entraine toujour des molécules de même sortes, mais où les molécules individuelles entrent et d'où elles sortent continuellement, de manière que la *forme* du corps vivant lui est plus essentielle que sa *matière*."

23. Garland E. Allen, *Life Science in the Twentieth Century* (New York: Wiley, 1975); Lynn K. Nyhart, *Biology Takes Form: Animal Morphology and the German Universities, 1800-1900* (Chicago: University of Chicago Press, 1995); Nicholas Jardine, James Secord, and Emma Spary, eds., *Cultures of Natural History* (Cambridge: Cambridge University Press, 1996); Paul Lawrence Farber, *Finding Order in Nature: The Naturalist Tradition from Linnaeus to E.O. Wilson*, Johns Hopkins Introductory Studies in the History of Science (Baltimore: Johns Hopkins University Press, 2000); Jan Sapp, *Genesis: The Evolution of Biology* (Oxford : Oxford University Press, 2003); Robert Richards, *The Romantic Conception of Life Science and Philosophy in the Age of Goethe* (Chicago: University Of Chicago Press, 2004); Sander Gliboff, *H.G. Bronn, Ernst Haeckel, and the Origins of German Darwinism: A Study in Translation and Transformation* (Cambridge: MIT Press, 2008).

24. This was famously stated by Michel Foucault, who argued that "life" and the science of "biology" were co-constructed when "life" and "non-life" became a more essential categorization than the older triumvirate of mineral-vegetable-animal; Michel Foucault, *The Order of Things: An Archaeology of the Human Sciences* (New York: Vintage Books, 1994), see 127–28, 157–162. Foucault's argument has led many scholars to examine how biologists think about life, notably in Sophia Roosth, "Life, Not Itself: Inanimacy and the Limits of Biology," *Grey Room* 57 (October 2014): 56–81; Stefan Helmreich and Sophia Roosth, "Life Forms: A Keyword Entry," *Representations* 112, no. 1 (November 2010): 27–53; Stefan Helmreich, *Silicon Second Nature: Culturing Artificial Life in a Digital World* (Berkeley: University of California Press, 1998). A different turn in ethnographic studies of science has consciously moved away from Foucault's simplified history, looking instead to how "life" is constituted in laboratory technique and experimental systems; two examples are Hannah Landecker, *Culturing Life: How Cells Became Technologies* (Cambridge: Harvard University Press, 2007); and Hans-Jörg Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube*, Writing

life, in a very Aristotelian sense, was also a kind of undifferentiated *matter*, as Mitchell and the *Britannica* understood it. Living matter and its vital phenomena were inextricable from one another, as inseparable as as water and wetness were to the Greek philosophers.[25] The biologists examined in this dissertation were certainly trying to create models of certain vital phenomena, but they were also interested in understanding what basic elements and materials living organisms were made of. Take, for example, the idea that biology should be "mechanistic" and that cellular phenomena should be explained in terms of protein "mechanisms." What, then, are the parts of such machines supposed to be made of? Is it better to think of a cellular mechanism in terms of its energy inputs and outputs, as changes in energetic and material state, or in terms that actually hint at crescent wrenches, grasping hands, gears, and flywheels?[26]

As an examination of the history leading to Schmidt's molecular vision of protoplasm, this dissertation will show that biologists often created their own theories of matter, inspired by and borrowing from modern physics, chemistry, and, after the 1890s, physical chemistry and colloid chemistry. At the same time very few biologists were exclusively "protoplasmologists," just as in this period few biologists were exclusively cell biologists. Most biologists fit their theories of matter and protoplasm into more immediate concerns. Therefore, following the general approach taken by Hans-Jörg Rheinburger, who has argued that major changes in science are usually generated within

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Science (Stanford: Stanford University Press, 1997). However, it has been pointed out many times, by biologists, historians, and philosophers alike, that "life" is simply not an operative concept in practice; see Michel Morange, *Life Explained*, trans. Matthew Cobb and Malcom DeBevoise (New Haven: Yale University Press, 2008).

25. "Of natural bodies some have life in them, others not; by life we mean self-nutrition and growth (with its correlative decay). It follows that every natural body which has life in it is a substance in the sense of a composite. But since it is also a body of such and such a kind, viz. having life, the body cannot be soul; the body is the subject or matter, not what is attributed to it. Hence the soul must be a substance in the sense of the form of a natural body having life potentially within it. But substance is actuality, and thus soul is the actuality of a body as above characterized." Aristotle, *De Anima* Book II, Part I, 412a, trans. John Alexander Smith in *The Works of Aristotle: De Anima* vol. 3 (Oxford: Clarendon Press, 1931), 520.

26. Andrew Reynolds, "The Cell's Journey: From Metaphorical to Literal Factory," *Endeavour* 31, no. 2 (June 2007): 65–70; and William Bechtel, *Discovering Cell Mechanisms: The Creation of Modern Cell Biology* (Cambridge: Cambridge University Press, 2008).

smaller material and technical "experimental systems," along the way this dissertation will point out where developments and changes in the protoplasm theory were driven by other, often more specific problems in biological theory and method.[27]

b. Chapter outline

The five chapters of this dissertation are divided roughly into two parts, which chronologically overlap. The first part, chapters 1–3, covers a history of the development of protoplasm theory, beginning from the 1840s as it was defined as the material bearer of life, and running through the 1920s as it was reconceived and studied as a colloidal aggregate. The second part, chapters 4 and 5, backtracks to the 1850s, following the history of micellar and molecular theory within biology, culminating in the molecularization of the cell and protoplasm in the 1930s.

But what was the protoplasm, and what was the difference between the protoplasm and the cell? Chapter 1 is an alternative reading of the history of the origin of the term "protoplasm" and the protoplasmic theory of life, building upon Gerald Geison and James Strick's histories of the same.[28] Rather than following the genesis of protoplasm theory as a bulwark against vitalism, or as an element of Victorian struggles about Darwinism and religion, this chapter will instead focus on why the protoplasm theory and the cell theory developed along separate intellectual trajectories, despite the fact both theories more or less pointed to the same microscopic objects. Drawing on George

27. Hans-Jörg Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube*, Writing Science (Stanford: Stanford University Press, 1997); Staffan Müller-Wille and Hans-Jörg Rheinberger, *A Cultural History of Heredity* (Chicago: University of Chicago Press, 2012); see also Matthias Dörries, "Life, Language, and Science: Hans-Jörg Rheinberger's Historical Epistemology," *Historical Studies in the Natural Sciences* 42, no. 1 (February 2012): 71–82.

28. Gerald L. Geison, "The Protoplasmic Theory of Life and the Vitalist-Mechanist Debate"; James Strick, "Darwinism and the Origin of Life: The Role of H. C. Bastian in the British Spontaneous Generation Debates, 1868-1873," *Journal of the History of Biology* 32, no. 1 (April, 1999): 51–92; and James Strick, *Sparks of Life: Darwinism and the Victorian Debates Over Spontaneous Generation* (Cambridge: Harvard University Press, 2000), especially ch. 5.

Lakoff and Mark Johnson's work on the role of metaphor and language in ontology, and specifically their distinction between *container*, *object*, and *substance*, this chapter will argue that the cell was metaphorically conceived as a bounded object or a container for other objects, while "protoplasm" became defined as the substance or material that living cells were made of.[29] By the end of the 1860s, biologists had, with caveats, redefined the cell as "a lump of protoplasm containing a nucleus," and the protoplasm as the so-called "physical basis of life."

Chapter 2 will show how biologists' attempts to study the protoplasm's structure culminated in a serious crisis over the legitimacy of cytological methods in the 1890s. Beginning in the 1870s, biologists had worked under the assumption that the methods they used for studying organ and tissue structure would also be fruitful for studying cellular and sub-cellular structure. Improvements in fixation, sectioning, and staining produced several blockbuster discoveries in histology and cytology. Yet over the course of the 1880s and through the 1890s a handful of biologists grew concerned that the strong fixative chemicals they used to preserve and reveal cellular structures were instead introducing unnatural artifacts at a sub-cellular level. In order to distinguish between what was a natural structure and what was a fixation artifact, these biologists began to apply cytological techniques to non-living, simple materials such as gelatin and egg white. This chapter will argue that the intensification of this argumentative strategy led to both a methodological and an ontological equivalence between living and non-living matter, as they became nearly indistinguishable under the microscope and in laboratory practice. In 1899, the English physiologist William Bate Hardy argued that the action of fixatives could be reinterpreted in terms of colloidal sol-gel precipitation reactions, and consequently that the protoplasm needed to be fundamentally reconceived as a colloid.

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29. George Lakoff and Mark Johnson, *Metaphors We Live By*, 2nd ed. (Chicago: University Of Chicago Press, 2003), 25–32, 55–68.

After Hardy's redefinition of the protoplasm as a colloid, biologists and physiologists rushed to embrace colloid chemistry to explain a broad range of protoplasmic and cellular phenomena — occasionally with great success, and just as often with retrospective embarrassment. Chapter 3 will argue that from about 1900 to 1940 biologists *physicalized* the life sciences, especially cell physiology, through their own demands for a more "physico-chemical" view of life and their potent enthusiasm for colloid chemistry. The strain of physics they embraced, however, was one that preferred the precision measurement of energy phenomena in the laboratory, and disdained speculations about invisible phenomena such as molecular structure. Thus, this chapter will examine the attitudes and epistemologies that colloid chemistry imparted to biology, especially the "descriptivist" energy physics grounded in a specific tradition of *fin-de-siècle* thermodynamics. As this chapter will explain, to speak of "molecular structure" in colloid physics was a contradiction in terms: molecules were not conceived to have any inherent structure, and structure was not thought of as arising from molecular-scale entities or forces. This chapter will explain why many "colloidic" biologists were skeptical about ideas of molecular structure, while at the same time biologists working on molecular theories might still find a home within colloid chemistry's disciplinary structures.

Chapters 4 and 5 will directly tackle Schmidt's molecular image of the protoplasm and the creation of a biological microworld, composed of atoms and molecules with distinct three-dimensional shapes, endowed with the powers of orientation and self-organization. Each chapter focuses on somewhat different molecular theories, though they are instrumentally and prosopographically linked. Chapter 4 is a history of the *micelle*, invented and defined by biologists in the nineteenth-century as a fundamental unit of material substance, and transformed by the botanist Hermann Ambronn (1856–1927) into a general theory of colloidal structure. While the term "micelle" today is usually only associated with tiny lipid spherules, the micellar theory originated in

the 1850s as a way of explaining the crystalline and optical properties of plant starch granules and cell walls. Through Ambronn's efforts, the micellar theory of molecular structure became an adjunct to colloid chemistry in the 1920s, thriving as a way of disaggregating colloids by visual and optical methods.

Ambronn developed the micellar theory alongside his development of polarized light microscopy as a useful tool for biologists, and much of chapter 4 will also be devoted to Ambronn's techniques, his imaginative use of this instrument, and his place in the history of scientific microscopy. Chapter 5 will begin by showing how W. J. Schmidt sought to expand the application of polarized light microscopy by lowering the mathematical barriers for its use in comparative anatomy. This chapter's main focus will be the development of the theory, and more importantly the iconography of *molecular orientation,* the idea that molecules with certain an intrinsic structures will orient themselves in energetically advantageous ways. This final chapter will argue that biologists in the mid-1930s used this kind of iconography to argue for and establish the existence of a biological microworld of atoms and molecules. The capacity to imagine that living matter is composed entirely of atoms and molecules was not necessarily achieved through mathematical physics or a deep understanding of structural chemistry, but rather by understanding a diagrammatic convention as a realistic representation of molecular reality.

c. *Molecules, biophysics, and the historiography of "molecular biology"*

A secondary theme that runs throughout this dissertation has to do with the *molecule* as an expression of a fundamental unit of organized matter. The "molecule" was an underdetermined concept in the nineteenth century despite its common use, and in the contexts that are important in this dissertation it was only in the years after the First World War that chemists' and physicists'

conceptions of the molecule converged, redefined as an assemblage of atoms with definite chemical structure *and* physical width, length, and breadth. In the historiography of the physical sciences it has become increasingly obvious that there is no single date for when molecules become "real," because there are so many different ways of thinking about molecules. In the history of chemistry, Ursula Klein has argued that molecular identity in organic chemistry took hold in the 1830s, as chemists standardized explanations of isomerism and substitution using Berzelian formulas. Alan Rocke in contrast points to the 1860s, when wooden chemical molecular models and Kekulé's theory of the benzene ring became widely accepted, and to the emergence of stereochemistry in the 1870s.[30] In the history of modern physics the issue is even more complicated, due to a prevailing positivist philosophy of physics that took hold around the *fin-de-siècle*, one which held atomic and molecular ideas in suspicion, even contempt.[31] Mary Jo Nye's classic monograph *Molecular Reality*, which has the best dust jacket of any history of science book ever published, explored how Jean Perrin convinced physicists of the reality of molecules in and around 1909. In her later work Nye has also argued that chemists and physicists today still think about atoms and molecules in different ways, despite the major phyiscal-chemical synthesis in the interwar period.[32]

Again, one of the primary contentions of this dissertation is that it was almost impossible to make arguments about the molecular structure of biological matter before the interwar period, and in the long chronology covered in this dissertation, the term "molecule" has no fewer than four

30. Ursula Klein, *Experiments, Models, Paper Tools*; Alan J. Rocke, *Image and Reality*, chapters 7 and 8. On stereochemistry and the origins of physical chemistry, see Peter J. Ramberg, *Chemical Structure, Spatial Arrangement: The Early History of Stereochemistry, 1874-1914* (Aldershot: Ashgate, 2003).

31. See Michael Stöltzner, "Vienna Indeterminism: Mach, Boltzmann, Exner," *Synthese* 119, no. 1/2 (1999): 85–111; David Lindley, *Boltzmann's Atom: The Great Debate That Launched a Revolution in Physics* (New York: Free Press, 2001), chapter 7; also see note 39, below.

32. Mary Jo Nye, *Molecular Reality: A Perspective on the Scientific Work of Jean Perrin* (London: Macdonald, 1972); and, *From Chemical Philosophy to Theoretical Chemistry: Dynamics of Matter and Dynamics of Disciplines, 1800-1950* (Berkeley: University of California Press, 1993). See also Kōstas Gavroglou and Ana Simões, *Neither Physics nor Chemistry: A History of Quantum Chemistry* (Cambridge: MIT Press, 2012).

different definitions. In chapters 1 and 2, a molecule was still just a tiny mass or part of some substance, synonymous with "particle" or "*Teilchen*," a simple definition that hews closely to its etymological roots; in the late nineteenth-century, the vast majority of biologists either ignored ideas of molecular structure or dismissed them as being too speculative, or too invisible. The colloid chemists and biologists to be discussed in Chapter 3 drew from kinetic theory, which held that a "molecule" was just a center of force, and from surface physics, which studied energy relations at the interfaces of two objects. For colloid physicists, then, the molecule was an abstract mass or particle with a surface, and was usually rendered mathematically as a sphere. The micelle, discussed in chapter 4, was a theory of particle structure that in some ways complemented the colloid chemical definition of the molecule, in that its size and shape could be indeterminate, so long as it was optically anisotropic (*i.e.,* an object whose optical properties change depending on the direction or alignment of the object). Only in chapter 5 will an idea of the molecule and of molecular structure appear that is familiar to us today: molecules with distinct length, width, breadth, atomic structure, and powers of self-organization and self-assembly into larger cellular structures.

Historians of biology have long noted that the meaning of the phrase "molecular biology" became hotly contested in the 1960s, having only entered common use in mid- to late-1950s — but by the end of the 1960s "molecular biology" most commonly gestured towards the molecular genetics that came out of Watson and Crick's "central dogma" of biological information and synthesis.[33] The first documented use of the phrase "molecular biology" was in a report from in 1938, written by Warren Weaver (1894–1978), director of the natural sciences division at the Rockefeller Foundation, who referred to it as "a relatively new field…in which delicate modern techniques are

33. On the chronology, see Gunther S. Stent, "That Was the Molecular Biology That Was," *Science* 160, no. 3826 (April 26, 1968): 390–95. Pnina Abir-Am has been especially good at dramatizing these conflicts: see "From Biochemistry to Molecular Biology: Dna and the Acculturated Journey of the Critic of Science Erwin Chargaff," *History and Philosophy of the Life Sciences* 2, no. 1 (1980): 3–60; and, "The Politics of Macromolecules: Molecular Biologists, Biochemists, and Rhetoric," *Osiris* 7 (1992): 164–91.

being used to investigate ever more minute details of certain life processes."[34] The historian Robert Kohler has long maintained that Weaver knew very little beyond this, and that the term indicated some vague confluence of biochemistry and biophysics; on the other hand, partisans like Erwin Chargaff wrote infamously cutting lines such as, "Molecular biology is the practice of biochemistry without a license."[35]

Yet, because the phrase "molecular biology" has seemed either obvious, meaningless, or contested, historians have preferred to explain the sudden appearance and dominance of molecular biology as a discipline, most notably by looking for the institutional and political settings that allowed Watson, Crick, and Franklin to bring together so many different disciplinary sensibilities to crack the genetic code. A particular concern for historians, and even an "obsession," has been the question of why so many physicists after the Second World War began to work on biological problems, and why the discovery of the DNA double helix was made largely by physicists who were outsiders to biology.[36] Although Robert Kohler and Nicholas Rasmussen have noted that post-war biophysics grew out of general physiology, they still see biophysics as being a largely postwar phenomenon, concentrated in the "biophysics bubble," whose inflation and collapse from 1945–60 was driven by the waxing and waning enthusiasms of the atomic age.[37] Despite the occasional efforts

34. Warren Weaver, "Molecular Biology: Origin of the Term," *Science* 170, no. 3958 (1970): 581–82.

35. Robert E. Kohler, "The Management of Science: The Experience of Warren Weaver and the Rockefeller Foundation Programme in Molecular Biology," *Minerva* 14, no. 3 (1976): 279–306; see also Kohler, *Partners in Science: Foundations and Natural Scientists, 1900-1945* (Chicago: University of Chicago Press, 1991), 299–302. The Chargaff line is quoted in Pnina Abir-Am, "The Politics of Macromolecules," 189; originally in Erwin Chargaff, "Amphisbaena," in *Essays on Nucleic Acids* (Amsterdam: Elsevier, 1963), 174–199.

36. Evelyn Fox Keller, "Physics and the Emergence of Molecular Biology: A History of Cognitive and Political Synergy," *Journal of the History of Biology* 23, no. 3 (September 1990): 389–409; Soraya de Chadarevian, *Designs for Life*, see especially ch. 3.

37. Nicolas Rasmussen, "The Mid-Century Biophysics Bubble: Hiroshima and the Biological Revolution in America, Revisited," *History of Science* 35, no. 109 (September 1997): 245–93, on 246; and Robert E. Kohler, *Partners in Science*, chapter 11. More problematically, most historians besides Kohler have treated general physiology and Jacques Loeb essentially as synonyms, despite the fact that was a very idiosyncratic and flawed scientist, whose powerful disciplinary vision collapsed before he died. See Philip J. Pauly, *Controlling Life: Jacques Loeb and the Engineering Ideal in Biology* (New York: Oxford University Press, 1987); and Gerald L. Geison, ed., *Physiology in the American Context, 1850-1940* (Bethesda: American Physiological Society, 1987).

of historians of biochemistry to highlight different molecules and pathways, the historiography of both biophysics and of molecules in biology is overwhelmingly post-war, centered on the genetic code and globular macromolecules, and focuses on the history of research in radioisotopes, x-ray crystallography, or electron microscopy.[38]

The pre-WWII biophysics that this dissertation will examine was very different from mid-century biophysics: biologists in the early twentieth century drew on a very different kind of physics, and did not refer to themselves as "biophysicists" as such. As this dissertation will show, during the first half of the twentieth century the kinds of physics many biologists engaged in were rooted not in the spectacular scientific discoveries of the twentieth century, but in the often in the philosophically and mathematically abstract and modernist physics of the late nineteenth century: thermodynamics, energetics, optics, and even ether physics.[39] One of the only historical examinations of molecular biology that seriously accounts for the epistemology and philosophy of pre-WWII physics is Phillip Sloan and Brandon Fogel's close reading of the 1935 "Three-Man Paper" (3MP) in genetics by Nikolai Timoféeff-Ressovsky, Karl Zimmer, and Max Delbrück.[40] The three attempted to explore the

38. Two recent examples are Angela N. H. Creager, *Life Atomic: A History of Radioisotopes in Science and Medicine* (Chicago; London: The University of Chicago Press, 2013); and Phillip R. Sloan, "Molecularizing Chicago, 1945–1965: The Rise, Fall, and Rebirth of the University of Chicago Biophysics Program," *Historical Studies in the Natural Sciences* 44, no. 4 (September 2014): 364–412. In the older literature, see: Robert Olby, *The Path to the Double Helix* (Seattle: University of Washington Press, 1974); Pnina Abir-Am, "The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology," *Social Studies of Science* 12, no. 3 (August 1982): 341–82; Pnina Abir-Am, "Themes, Genres and Orders of Legitimation in the Consolidation of New Scientific Disciplines: Deconstructing the Historiography of Molecular Biology," *History of Science* 23 (March 1985): 73–117; Robert E. Kohler, *Partners in Science*; Lily E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology*, (Oxford: Oxford University Press, 1993); Paul Rabinow, *Making PCR: A Story of Biotechnology* (Chicago: University of Chicago Press, 1996); Lily E. Kay, *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford: Stanford University Press, 2000). For alternative views from the history of biochemistry, see for example Joseph S. Fruton, *Proteins, Enzymes, Genes: The Interplay of Chemistry and Biology* (New Haven: Yale University Press, 1999); Joseph S. Fruton, *A Skeptical Biochemist* (Cambridge: Harvard University Press, 1992).

39. On modernism in *fin-de-siècle* physics see: Deborah R. Coen, *Vienna in the Age of Uncertainty: Science, Liberalism, and Private Life* (Chicago: University of Chicago Press, 2007); Richard Staley, "The Fin de Siècle Thesis," *Berichte Zur Wissenschaftsgeschichte* 31, no. 4 (December 2008): 311–30; and Paul Forman et al., eds., *Weimar Culture and Quantum Mechanics: Contemporary Perspectives on the Forman Thesis* (London: Imperial College Press, 2011).

40. Phillip R. Sloan and D. Brandon Fogel, eds., *Creating a Physical Biology: The Three-Man Paper and Early Molecular Biology* (Chicago: The University of Chicago Press, 2011).

material basis of genes and mutations by irradiating *Drosophila* fruit flies with x-rays, and correlating the x-ray dose (in röntgens) with the number of biological mutations that resulted — all while not being sure of what genes were, how they might interact with x-rays, or what counted as a mutation. Sloan, Fogel, et al., note that this abstract, quantitative approach to a hypothetical material basis of heredity was well grounded in contemporary philosophy of physics, including the 1920s and '30s discourse of "complementarity" in which Delbrück and his mentor Niels Bohr took part.

The 3MP was representative of another phenomenon that recurs frequently throughout this dissertation: the blurry lines between various disciplines and subfields within the biological and physical sciences. This was certainly the case in the history of genetics, and this was true too of the history colloid chemistry and the history of protoplasm research. Protoplasmic structure and function were problem areas that were open to many different approaches, and protoplasm research was never monopolized by plant physiologists, botanists, zoologists, or anatomists, just to name a few possible disciplinary demarcations from the nineteenth century. For the most part this dissertation will not try to clarify the disciplinary lines between, for example, botany and plant physiology, though the labels will occasionally be used to help identify individuals and hint at some of their diffuse disciplinary priorities (*e.g.,* structure, function, classification). Methodologically, this dissertation focuses on the community of diverse scientists who sought to understand the relationship between ideas of life and ideas of matter, following citations within published books and periodicals to trace common reference points, conversations, and arguments within this loosely defined problem area. As a result, the analysis here is on individual scientists and the specific methods they brought to bear on protoplasm, and not too much should be read into the disciplinary labels when they appear. For example, William Bate Hardy, a key figure in chapters 2 and 3, was a physiologist who was intimately concerned with anatomical structure, but during the First World

War his research permanently shifted towards the physics and chemistry of lubrication. Hardy and many of the figures in this dissertation found themselves migrating from one discipline to the next, some more easily than others.

Another disciplinary issue that will face readers of this dissertation is that during this period, spanning the late nineteenth and early twentieth centuries, the very nature of disciplinarity was changing within the biological and physical sciences. In biology, disciplines in the nineteenth century were largely taxa-based, whereas in the twentieth century new disciplines arose that were defined around biological problems.[41] Genetics, embryology, and even protoplasm research were among these new disciplinary divisions, and the existence of genetics or protoplasm research as disciplinary specialties never precluded botanists or zoologists from participating in those conversations. In the history of colloid chemistry, these formal identities were even less clear, and this lack of clarity was reflected in the changing fortunes of the very terms "colloid chemistry" (*"Kolloidchemie"*) and "colloid science" (*"Kolloidwissenschaft"*). In this dissertation, the terms "colloid chemistry," "colloid science," and "colloid physics" will be used completely interchangeably, reflecting the in-between, interdisciplinary status of its practitioners. Colloid science was a breakaway branch of physical chemistry, a discipline that was itself caught between physics and chemistry, and a discipline that had once called itself "general chemistry" (*"Allgemeine Chemie"*) before settling on a name that better reflected its grounding in thermodynamics and energy physics.[42] As some practitioners began to refer to the discipline as "colloid science," to better reflect the discipline as a distinct field, others maintained the phrase "colloid chemistry" to reflect its historical origins in chemistry and physical chemistry.[43] The precise nature of these disciplinary labels is even more blurry when one considers

41. Kristin Johnson, "The Return of the Phoenix: The 1963 International Congress of Zoology and American Zoologists in the Twentieth Century," *Journal of the History of Biology* 42, no. 3 (August 2008): 417–56.

42. John W. Servos, *Physical Chemistry from Ostwald to Pauling: The Making of a Science in America* (Princeton: Princeton University Press, 1990).

that the founder of colloid chemistry, Thomas Graham, was professionally an inorganic chemist, worked with many organic substances in his research, and performed research in the physics of diffusion just as often as he did research in inorganic acids.[44] The diverse and polyglot nature of colloid science meant that its practitioners were relatively flexible with such labels; "colloid science" was a way of calling attention to the relative independence of the field, which came from its focus on a defined set of material properties and problems, but it was also a way of showing that colloids were studied by physicists, chemists, and biologists alike. The phrase "colloid physics" will be used here slightly anachronistically to emphasize the close connection between colloid chemistry and nineteenth century energy physics, but not too much should be made of it. Colloid chemistry, like many areas of the physical sciences, brought together many older approaches and techniques to address novel problems.

Such historical and disciplinary diversity within the physical sciences was especially true when it came to definitions of the molecule. There were many different ideas and ways of thinking about molecules in the biological sciences besides those that led to the discovery of the DNA double-helix and the Central Dogma, depending on how any one scientist understood "molecular" and "biology." This was a particular hobby horse one of the elder statesmen of American biology, the MIT biologist Francis O. Schmitt (1903–1995), who late in life would complain, "They call all this 'molecular biology.' Well now that's a very, *brooaaad* feeling, and it's in a sense preemptive terminology, to those of us who started the field more than a half century ago. We were molecular biologists *then*," in the 1930s and '40s.[45] Molecular biology in Schmitt's "then" was the study of cells

43. Ernst A. Hauser, "The History of Colloid Science: In Memory of Wolfgang Ostwald," *Journal of Chemical Education* 32, no. 1 (1955): 2–9; see also Klaus Beneke, *Über 70 Jahre Kolloid-Gesellschaft: Gründung, Geschichte, Tagungen* (Kiel: Institut für Anorganische Chemie der Christian-Albrechts-Universität Kiel, 1996).

44. George B. Kauffman, "Graham, Thomas," in *Complete Dictionary of Scientific Biography*, vol. 5 (Detroit: Charles Scribner's Sons, 2008), 492–95.

45. Francis O. Schmitt: Microscopy Society of America Oral History Project, interview by Sterling Newberry, 1990.

and protoplasm, the living matter, grounded in the idea that life could be studied by investigating its material basis.

Chapter 1: The "Cell" and "Protoplasm" as Container, Object, and Substance, 1838–1861

Without a hint of irony, the eminent American cytologist Edmund Beecher Wilson began the first chapter of his great 1896 textbook, *The Cell in Development and Inheritance*, with a plaintive plea, asking all students of science to stop using the word "cell." "The term 'cell' is a biological misnomer," Wilson cried out, "for whatever the living cell is, it is not, as the word implies, a hollow chamber surrounded by solid walls. The term is merely an historical survival of a word casually employed by botanists of the seventeenth century to designate the cells of certain plant tissues which, when viewed in section, give somewhat the appearance of a honeycomb."[1] Wilson's reproach of cytology students' grievous terminological and conceptual errors emphasized the correctness of the last few decades of research and theory in biological science, and he proffered the more correct and exacting definition used by only the best and the brightest of students: "The cell [has come] to be defined by Max Schultze and Franz Leydig as a *mass of protoplasm containing a nucleus*, a morphological definition which remains sufficiently satisfactory even at the present day." He continued, "Nothing could be less appropriate than to call such a body a 'cell'; yet the word has become so firmly established that every effort to replace it by a better has failed, and it probably must be accepted as part of the established nomenclature of science."[2]

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1. Edmund B. Wilson, *The Cell in Development and Inheritance*, 1st ed. (New York: MacMillan, 1896), 13. Wilson's textbook had a strong predecessor in Oscar Hertwig's *Die Zelle*, published in German in 1893 and translated into English two years later. "It is evident that the term 'cell' is incorrect. That it, nevertheless, has been retained, may be partly ascribed to a kind of loyalty to the vigorous combatants, who, as [Ernst von] Brücke expresses it, conquered the whole field of histology under the banner of cell theory." Oscar Hertwig, *The Cell: Outlines of General Anatomy and Physiology*, trans. M. Campbell (London: Swan Sonnenschein & co., 1895), 8.

2. Edmund B. Wilson, *The Cell in Development and Inheritance*, 14. In a footnote Wilson suggested that Julius Sachs' neologism *energid*, "*i.e.* the nucleus with that portion of the active cytoplasm that falls within its sphere of influence," was more appropriate in both morphological and physiological senses, and that, "It is to be regretted that this convenient and

Despite the cell theory's now-hallowed status as a watershed moment in the history of science, in its first decades both the "cell" and "protoplasm" concepts were simultaneously revered and treated with some suspicion. In 1838 the botanist Matthias Jacob Schleiden (1804–1881) articulated a cell theory that united the plant kingdom under a single principle of form and development, and a year later his colleague Theodor Schwann (1810–1882) generalized the cell theory as both a unifying theory of life and as a foundation for the study of the new science of biology. The cell theory was troubled enough that by its centenary in 1939, American cytologist Edwin Conklin (1863–1952) was traveling across the United States arguing that Schleiden and Schwann's scientific legacies were best respected by expunging their names from cell theory altogether.[3] Yet, of the rough replacements for the *cell*, only *protoplasm* managed to enter common parlance, and protoplasm never fully replaced the cell. Despite the fact that they roughly corresponded with the same material entity, protoplasm theory always sat somewhat orthogonal to cell theory, both in its historical trajectory and in its contemporary scientific use. As Jan Sapp has argued, "Stories about the origins of cell theory are puzzling," in part because what culminated in Schleiden and Schwann's theory in 1839 was a synthesis of many smaller parts, each with its own origin and history.[4] But what came after 1839 was just as tangled, and Schwann's hoped-for grand synthesis of biological theory productively generated many new ways of seeing, conceptualizing, and even naming cells and their parts. Most biologists accepted that the terms *cell* and *protoplasm* had very different meanings, even as they seemed to share a single material referent.

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appropriate term has not come into general use."

3. Edwin G. Conklin, "Predecessors of Schleiden and Schwann," *The American Naturalist* 73, no. 749 (November 1, 1939): 538–546, on 546; and Edwin G. Conklin, "Cell and Protoplasm Concepts: Historical Account," in *The Cell and Protoplasm*, ed. Forest Ray Moulton (Washington, D.C.: The Science Press, 1940), 6–19, on 13.

4. Jan Sapp, *Genesis: The Evolution of Biology* (Oxford: Oxford University Press, 2003), 75.

This chapter will argue that the choice of ideas and the outright confusion in terminology in the histories of the cell and the protoplasm concepts stems from the largely hidden ontological commitments that were implied by various key terms in cellular anatomy. Every biologist who attempted to reform cell theory after Schleiden and Schwann had their own aims and interests, and these differences often manifested themselves in their choice of terminology. On the one hand, the epistemological commitments of cell researchers after 1839 were relatively consistent: by and large they were interested in finding a unified theory of life, creating better taxonomic rules, and crafting general laws to explain the relationship between anatomical structure and physiological function. On the other hand, it was their *ontological* commitments — their claims about primary materials and objects — that shifted and changed, and that were an area of fruitful speculation and debate.[5] By 1896 Wilson was well aware that his insistence on this terminological shift from "cell" to "protoplasm" changed the nature of thing referred to, by emphasizing the mass of protoplasm over and above the boundary of the cell. As this chapter argues, a conceptual displacement of the cell concept by the protoplasm concept in the mid-nineteenth century was a significant ontological shift, much more consequential than a simple matter of incorrect vocabulary.

This chapter draws on the terminology developed by George Lakoff and Mark Johnson to describe different kinds of ontological metaphors, namely the distinction between *container*, *object* (or *entity*), and *substance*. Whereas the cell was initially conceived as a minimal unit of life defined through its boundary, protoplasm was defined as the substance from which living cells were made. Lakoff and Johnson's distinction between container, object/entity, and substance is subtle and crucial, and explains why the cell concept and protoplasm concept could point to the same thing in the

5. The term "ontology" has come under intense scrutiny in science studies, (see especially the June 2013 special issue of *Social Studies of Science*), but here I am using it in the classical philosophical sense of asking questions about "what is" or "what exists," as opposed to a classical examination of epistemology, of "what is known" or "how it is known." In STS the current vogue is in examining the "enactment" of ontology, which is not my aim here.

microscope use two separate theories to describe it. Container metaphors define in-out relationships and orient a spatial field: a cell is defined by the boundary or membrane, holding its contents (nucleus, starch granules, vacuoles) within itself against the environment and other cells. The cell is also an individuated object/entity, in that one cell can be compared against other cells or other objects; in the same sense, one could say a bathtub is defined by its ability to hold water as a physical and spatial boundary, but a bathtub is also a object that can be counted, repaired, sold, etc. In contrast, protoplasm was always defined as a kind of substance, formless matter from which living cells were made, and endowed with specific properties, and defined as the material seat of specific physiological processes. (In a simpler vein, lead might be defined by its malleability, toxicity, or its use.) Container, object/entity, and substance metaphors serve different cognitive purposes in specific contexts, and this was certainly the case with the origin of the cell and protoplasm concepts in the mid-nineteenth century. While Schleiden and Schwann had initially discussed cells in terms of boundaries and membranes, later biologists, as this chapter will show, shifted the theoretical and epistemological framework towards discussions of the objects within the cell, and later the substances that made up different parts of the cell.

This chapter travels a well-worn path in the history of biology, best known in Gerald Geison's classic 1969 history of protoplasm theory and Victorian vitalist-mechanist debates, and James Strick's 1999 study of the arguments over the possibility of spontaneous generation within Darwinian evolutionary theory.[6] Geison showed how the term "protoplasm" developed in German biology to refer to a living substance common in plants and animals, and how T. H. Huxley (1825-1895) transformed the term into the "physical basis of life" in 1868. Strick builds on Geison's history, examining how protoplasm became controversial within Huxley's circle of Darwinists, and how

6. Gerald L. Geison, "The Protoplasmic Theory of Life and the Vitalist-Mechanist Debate," *Isis* 60, no. 3 (October 1969): 273–92.

Huxley and his supporters found themselves defending a sharp boundary between life and non-life.[7] While this present chapter revisits Huxley in its conclusion, it will more closely follow Geison's history of the early German development of protoplasm theory, as well as Thomas Hall's rather rather dated history of general physiology, *Ideas of Life & Matter*, published the same year.[8] This dissertation and Hall's two-volume history follow some of the same themes and questions — what Hall calls the "life-matter problem." But whereas Hall, Geison, and Strick see the history of the protoplasm concept as an attempt to redefine life, or as an attempt to re-focus cell studies on the interior of the cell, the present chapter argues that protoplasm theory came out of arguments about what kind of substance or material entity life could be: inherent in an object or form, or inherent in a substance from which objects or forms are made. And whereas J. Andrew Mendelsohn has argued that changes to the cell theory were often localized to the particular objects biologists were looking at — cork, cartilage, eggs — this chapter will show that protoplasm theory developed out of localized debates about what *kind* of things cells were, debates driven by scientists who disagreed with Schleiden and Schwann's way of emphasizing the cell's importance.[9]

The debates that created the cell theory were from the very beginning battles over proper terminology and the correct identification of parts of living tissues under the microscope, and these continued through the ascendency of protoplasm theory toward the end of the nineteenth century.[10] What makes it both difficult and fascinating to tell a history of the cell and protoplasm concepts at the same time is that they referred to many of the same phenomena. Yet investigators claiming to

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7. James Strick, "Darwinism and the Origin of Life: The Role of H. C. Bastian in the British Spontaneous Generation Debates, 1868-1873," *Journal of the History of Biology* 32, no. 1 (April 1999): 51–92; Strick's extended account is *Sparks of Life: Darwinism and the Victorian Debates Over Spontaneous Generation* (Cambridge: Harvard University Press, 2000).

8. Thomas S. Hall, *Ideas of Life and Matter: Studies in the History of General Physiology, 600 B.C.-1900 A.D.* (Chicago: University of Chicago Press, 1969), vol. 2, chapters 41 and 42. Both Hall and Geison were old enough that in secondary school they were likely still taught that protoplasm was the material basis of life.

9. J. Andrew Mendelsohn, "Lives of the Cell," *Journal of the History of Biology* 36, no. 1 (2003): 1–37, on 17.

10. Jan Sapp, *Genesis*, 75–81, 87–88.

study cells or protoplasm often examined different species or anatomical objects, and they followed distinct disciplinary agendas. So when Conklin offered his history of the cell and protoplasm concepts for one of the AAAS's centenary celebrations of the cell theory, he wisely warned friends and colleagues to keep in mind "the multitude of persons or a multiplicity of causes," before discussing twenty-three major characters (and dozens more minor ones) in the history of cell and protoplasm theory.[11] This chapter will endeavor to weave together the linguistic, technical, and a few of the visual aspects of microscopic biology to show how biologists thought about matter in the middle of the nineteenth century, and to demonstrate that the incongruous rise of both cell and protoplasm theories together was a result of the multiple ontological foundations available to biologists.

a. Schleiden, Schwann, and the mechanics of cell growth

In the nineteenth century, protoplasm was just one of a handful of primordial substances biologists considered, and some date to the mid-eighteenth century, if not earlier. A list given by historian Ohad Parnes includes Albrecht Haller's *tela celulosa* (1754), Theophile Bordeu's *tissu muquex* (1767), Friedrich Tiedemann's *Gallerte* (1808), Samuel Christian Lucae's *Zellstoff* (1810), Ignaz Döllinger's *Tierstoff* (1819), Nees von Esenbeck's *Schleim* (1814), Christian Pander's *Keimhaut* (1817), Karl Ernst von Baer's *Grundmasse* (1824?) and Carl Krause's *Urtierstoff* (1833) — all of them more or less liquid or mucilaginous, and all of them a primordial substance from which embryos or

11. Edwin Conklin, "Cell and Protoplasm Concepts," 6. Conklin's essay has been a cornerstone for the historiography of cell theory, and the essay has an iconoclastic wit that has been a feature of the literature ever since. "In spite of my age, which may seem venerable to some of you, I was not in at the birth of the cell theory and I have had to rely largely on the literature in preparing the earlier part of this address." The lecture appears to have been given at the AAAS's symposium held at Stanford University in June 1939. An earlier and shorter version was delivered to an AAAS meeting in Richmond, Virginia on December 27, 1938, part of which also was to celebrate the cell theory centennial. Most of the papers from the Richmond meeting were published in *The American Naturalist*, in issues 739 (1939) and 740 (1940).

tissues are formed.[12] To this list one might also add protoplasm: in 1839, the Czech anatomist Jan Evangelista Purkyně (1787–1869) used the term to refer to the formative matter responsible for embryonic development. Exactly what Purkyně meant when he invoked the vaguely biblical word is now obscure, however, and references to his usage of the word only point to a published summary of his remarks and demonstrations given to the *Schlesische Gesellschaft für vaterländische Kultur*.[13]

Parnes as well as Staffan Müller-Wille have argued that Theodor Schwann's canonization of cell theory in 1838–39 marked a dramatic "epistemological schism" in the study of life: whereas before 1839 biologists conceived of life and vital processes as a tension between generative and corruptive *forces* acting *upon* matter, after 1839 biologists conceived of vital processes as obeying laws inherent *within* the kind of material that creates cells and tissues.[14] Thus according to Parnes, before 1839 all of the living substances listed in the paragraph above were understood to be inert, primordial substances out from which tissues and organisms are wrought through the agency of vital

12. Ohad Parnes, "The Envisioning of Cells," *Science in Context* 13, no. 1 (March 2000): 71–92.

13. cf. Gerald L. Geison, "The Protoplasmic Theory of Life and the Vitalist-Mechanist Debate," and John R. Baker, "The Cell-Theory: A Restatement, History, and Critique, Part II," *Quarterly Journal of Microscopical Science* 90, no. 9 (1949): 90–91. Baker quotes Purkyně at length to argue that he was trying to draw an analogy between plant and animal development, but on closer reading it is not clear what part of the animal embryo Purkyně's "protoplasma" referred to. Purkyně's own goal in 1839 was to make the case that elementary animal units (*Bildungselementen*) could be analogous to Schleiden's plant cells, and he showed some hesitation as to whether animals were universally cellular in composition. For the report on Purkyně's demonstration, see "Über die Analogieen in den Struktur-Elementen des thierischen und pflanzlichen Organismus," *Uebersicht der Arbeiten und Veränderungen der schlesischen Gesellschaft für vaterländische Kultur, im Jahre 1839*, (Breslau: Graß, Barth, und comp., 1840), 81–83.

As another intriguing coincidence which has not been explained, Purkyně was likely well aware that the Latin term *protoplastus* was a Catholic liturgical term that referred to Adam, and which could be translated as "first creation." Purkyně had joined the Piarists after completing his *Gymnasium* education, but left the Catholic order shortly before he was to be ordained, in search of a different direction in life. There is no indication of whether this religious meaning was known to later, more materialistic scientists who adopted the term, although it is conceivable that the liturgical meaning was one reason why T. H. Huxley so enthusiastically embraced a more materialistic conception of protoplasm in the late-1860s. See Rudolf Heidenhain, "Purkinje, Johannes Evangelista," *Allgemeine Deutsche Biographie* Bd. 26 (Bayerische Staatsbibliothek, 1888).

14. Ohad Parnes, "The Envisioning of Cells"; and Staffan Müller-Wille, "Cell Theory, Specificity, and Reproduction, 1837–1870," *Studies in History and Philosophy of Biological and Biomedical Sciences* 41, no. 3 (2010): 225–31. For a summary of some views on these vital forces, as well as a counterpoint to Parnes, see Georges Canguilhem, "Cell Theory," in *A Vital Rationalist: Selected Writings from Georges Canguilhem*, ed. François Delaporte, trans. Arthur Goldhammer (New York: Zone Books, 1994), 161–77.

forces. Schwann's innovation was to relocate this agency to the material basis of the cell itself, which he called the "*cytoblastema*." Parnes ends his historical account with Schwann, while Müller-Wille treats Darwin and Mendel in light of Parnes' interpretation of Schwann, showing that Darwin understood organic development as a product of the cells' own agency. Parnes and Müller-Wille do not comment on whether or not this shift from vital forces to material causes was only an epistemological shift, given that Kant and Blumenbach had granted living or generative forces some degree of ontological status, as analogous to Newtonian or Leibnizian gravitational force.[15] Nor do they discuss the fate of Schwann's cytoblastema theory after 1839, *i.e.,* the idea that there was a cell-creating matter, and thus how this "epistemological schism" may have persisted within debates about the cell theory itself after 1839. Schleiden and Schwann's focus was on the relationship between cells and the organism, but in articulating a theoretical and universal "cell" they also needed to address how cells were made, and what cells were made of. Rather than search for a grand epistemological scheme as Parnes and Müller-Wille have done, this chapter will examine the ontological commitments and ideas of matter of the cell theorists who came after Schleiden and Schwann. In the smaller controversies after 1839, the many debates about cell theory became restricted to cells themselves or cell-scale phenomena rather than grander problems of organic form.

The Scheiden-Schwann cell theory's powerful statement that all life is essentially cellular was not what came under immediate criticism. Rather, through the 1840s and '50s Schleiden and Schwann were mainly criticized for their description of cell genesis. Their much-maligned theory of "free cell formation" held that cells formed through a sort of condensation of substances; for Schleiden this occurred within the cell, for Schwann cell genesis happened outside of the cell. In his original 1838 essay, "Contributions Towards Phytogenesis," Schleiden merely called this substance

15. See chapters 1–2 of Nicholas Jardine, *The Scenes of Inquiry: On the Reality of Questions in the Sciences* (Oxford: Clarendon Press, 1991).

"gelatin" (*Gallerte*), noting that, "It is this gelatin which is ultimately converted by new chemical changes into the actual cellular membrane, or its thickening layers, and into vegetable fibre."[16] (Schwann would call this substance "cytoblastema," a terminological innovation that Schleiden absorbed only in 1842.) Schleiden described a sequence of events where a nucleus or "cytoblast" appeared within the "gelatin" and formed a membrane around itself, creating the young cell within the parent cell. In 1838 Schleiden had little more to say about this gelatinous material precursor to cell genesis, but in his 1842 textbook *Principles of Scientific Botany* Schleiden described cytoblastema as consisting of "sugar, dextrin, and mucus (protein)." He went on to add that little else was known about the chemical composition of the cytoblastema: "Of the nature of the fluid in and out of which the cells originate, we are not yet perfectly cognisant. This much we know, that in some cases…a solution of sugar is present; and, as far as may be decided by the action of alcohol, this is mixed with gum (dextrin?) [*sic*]. The constant presence of a nitrogenous substance is also necessary."[17]

The material and mechanical process that interested Schleiden was growth, which he defined strictly as cellular growth. In a rather long digression on the topic, he began by complaining that recent botanists had erroneously thought of growth as a force or a law unto itself: for example, he accused one botanist of suggesting that, "The law of the longitudinal growth of the internodes is, to grow *inter se*, or from above downwards."[18] The scientifically appropriate way to explain growth, Schleiden insisted, was to name the growing entities in question and give an explanation for how they grew. So, in describing the growth of plants, Schleiden offered: "The plant unfolds itself by the

16. Matthias Schleiden, "Contributions to Our Knowledge of Phytogenesis," trans. William Francis, *Taylor's Scientific Memoirs* 2, no. 6 (1841): 281–312, on 286–87. The original German article is: Matthias Schleiden, "Beiträge zur Phytogenesis," Müllers *Archiv für Anatomie, Physiologie, und wissenschaftliche Medizin* 5 (1838): 137–176, on 144.

17. Matthias Schleiden, *Principles of Scientific Botany*, trans. Edwin Lankester (London: Longman, Brown, Green, and Longmans, 1849), 31. The original German is: Matthias Schleiden, *Grundzüge der wissenschaftlichen Botanik* (Leipzig: Wilhelm Engelmann, 1842), 192. "Ueber die Flüssigkeit, in und aus der die Zellen entstehen, sind wir freilieb, noch lange nicht im Klaren. So viel wissen wir, dass in einigen Fällen…bestimmt eine Zuckerlösung, und, wie aus dem Verhalten gegen Alkohol hervorzugehen scheint, vermischt mit Gummi vorhanden ist."

18. Matthias Schleiden, "Contributions to Our Knowledge of Phytogenesis," 298; in the German 159.

expansion and development of the cells that are formed."[19] As for cells themselves, "It is quite an essential law that every cell…must occur in the form of a minute vesicle, gradually expanding to the size in which we find it in the developed state."[20] Schleiden continued to use an eighteenth-century language to describe two different modes of cell growth: intussusception (Latin *intussusceptio*), the cell growing from within itself (the aforementioned "unfolding"); and juxtaposition (Latin *juxtapositio*), growth of the cell through a depositing of new layers on the outside of the mature cell membrane.[21] Armed with this scientific understanding of the two kinds of growth, and further equipped with a theory of the cellular structure of plants, Schleiden argued that a truly scientific botany comprehended three different kinds of growth: the production of cells, the expansion of cells already formed, and the thickening of the walls of cells. The latter two were exclusive to plants, perhaps even defining the plant kingdom, and "can never in any form, not even a remote one, occur in crystals or in animals."[22]

Schwann expanded upon Schleiden's theory to argue that cellular growth was a form of crystallization, precisely what Schleiden had disavowed. Schwann famously devoted the concluding thirty-seven pages of his *Microscopical Researches* towards expanding Schleiden's discussion of the "laws" of cell growth, making a tight connection between the composition of the cytoblastema and the supposed crystallization of new cells. Schwann ultimately argued that "organisms are nothing but the form under which substances capable of imbibition crystallize," and that by extension all organismal growth followed those laws of crystallization.[23] He conceived of the crystallization process

19. *ibid.,* 300; in the German 161. The quote continues: "It is this phænomenon especially, altogether peculiar to plants, which, because it results from their composition of cells, can never in any form, not even a remote one, occur in crystals or in animals."

20. *ibid.,* 291; in the German 150.

21. *ibid.,* 299; in the German 160. The interjection of Latin suggests the deeper historical roots of Schleiden's essay. See Norma E. Emerton, *The Scientific Reinterpretation of Form* (Ithaca: Cornell University Press, 1984).

22. Matthias Schleiden, "Contributions to Our Knowledge of Phytogenesis," 300; in the German 161.

23. Theodor Schwann, *Microscopical Researches into the Accordance in the Structure and Growth of Animals and Plants*,

much in the same way that Buffon, Linnaeus, and many others in the eighteenth century did: as layers of two-dimensional particles or molecules deposited onto a central nucleus, analogous to the way lacquerware is made by depositing successive layers of lacquer onto a wooden or bamboo form.[24]

> A small corpuscle (the nucleolus) is the earliest formation, that [*sic*] a stratum (the nucleus) is first deposited around it, and then subsequently a second stratum (substance of the cell) around this again. The separate strata grow by the reception of new molecules between the existing ones, by intussusception, and we have here an illustration of the law, in deference to which the deposition takes place more vigorously in the external part of each stratum than it does in the internal, and more vigorously in the entire external stratum than in the internal. In obedience to this law it often happens that only the external part of each stratum becomes condensed into a membrane (membrane of the nucleus and membrane of the cell), and the external stratum becomes more perfectly developed to form a cell, than the nucleus does.[25]

The details here are essentially the same as with Schleiden: the juxtaposition of layers (Schwann used the Latin synonym *appositio*) on the formative nucleus, followed by both the intussusception of the middle layers of the cell and the further juxtaposition of the outer, primary membrane. Historians have disagreed about whether Schwann's theory of cellular crystallization was merely an instrumentally useful hypothesis, or whether instead it was a strong materialist stance against so-called "vitalist," *naturphilosophisch*, or teleological theories of growth — it could conceivably be both.[26] What is indisputable, however, is that at a minimum Schwann went to great lengths to argue that there were natural laws (*Gesetze*) governing cell growth that operated by necessity

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trans. Henry Smith (London: The Sydenham Society, 1847), 215. The original German is Theodor Schwann, *Mikroskopische Untersuchungen ueber die Uebereinstimmung in der Struktur und dem Wachsthum der Thiers und Pflanzen* (Sanders'chen Buchhandlung, 1839), 257.

24. Norma Emerton, *The Scientific Reinterpretation of Form*, 236–37.

25. Theodor Schwann, *Microscopical Researches*, 180; in the German 213.

26. See Everett Mendelsohn, "Physical Models and Physiological Concepts: Explanation in Nineteenth-Century Biology," *British Journal for the History of Science* 2, no. 3 (1965): 201–19; and Russell C. Maulitz, "Schwann's Way: Cells and Crystals," *Journal of the History of Medicine and Allied Sciences* 26, no. 4 (1971): 422–37. Mendelssohn argues that Schwann was motivated by his antagonism towards *Naturphilosophie* and various kinds of teleological theories of growth, while Maulitz sees Schwann as more cautious and philosophically oriented towards instrumentalism in his theory-making. As Maulitz points out, Schwann himself hedged his argument as hypothetical or merely instrumental in the last sentences of his book, noting that there was "very much that is uncertain and paradoxical." For further perspectives on Schwann's materialism see also Everett Mendelsohn, "Cell Theory and the Development of General Physiology," *Archives internationales d'histoire des sciences* 65 (1963): 419–29; J. Lorch, "The Charisma of Crystals in Biology," in *The Interaction Between Science and Philosophy*, ed. Samuel Sambursky and Yehuda Elkana (Atlantic Highlands: Humanities Press, 1972), 445–61; and François Duchesneau, *Genèse de la théorie cellulaire* (Montréal: Bellarmin, 1987).

(*Nothwendigkeit*), even if some parts of such a law remained unclear. After a lengthy consideration of the genesis of inorganic crystals and organic "crystals capable of imbibition" (*imbibitionsfähiger Krystalle*), Schwann asked a well-hedged rhetorical question,

> Should we not then be justified in putting forth the proposition, that the formation of the elementary parts of organisms is nothing but a crystallization of a substance capable of imbibition, and the organism nothing but an aggregate of such crystals capable of imbibition? To advance so important a point as absolutely true, would certainly need the clearest proof; but it cannot be said that even the premises which have been set forth have in all points the requisite force. For too little is still known of the cause of crystallization…[27]

Schleiden in 1838 would certainly have agreed with Schwann's last point: Schleiden had earlier argued that intussusception, at least, is a "phenomenon…altogether peculiar to plants, which, because it depends upon the fact of their being composed of cells, can never occur in any, not even the most remote form in crystals or animals."[28] Whether crystallization was an appropriate analogy to explain organic growth would drive many of the transformations of cell theory through the rest of the 1840s.

b. Hugo von Mohl's Primordialschlauch

This vision of cell genesis by depositing layers of material would become a central point of contention by cell theorists later in the 1840s, and it is why later generations of cell researchers would come to see Schleiden and Schwann as being too focused on the membrane and nucleus. In addition, whereas Schleiden and Schwann spent much of their work in 1838–39 on multicellular organisms that had obvious cellular tissues, the controversial nature of Schwann's claims about cellular growth opened a new debate on the growth and reproduction of individual cells. By the time Hugo von Mohl (1805–1872) "gave the word 'protoplasm' its modern biological meaning" in a series

27. Theodor Schwann, *Microscopical Researches*, 212–13; in the German 254.

28. Matthias Schleiden, *Principles of Scientific Botany*, 251; in the German 161.

of papers published in 1844–46, Schleiden had already done the intellectual work to establish the cell as an essential topic in laboratory botany.[29] In the 1844 article, von Mohl argued for the existence of an object, the "*Primordialschlauch*" or "primordial utricle," that was responsible for creating the boundary that defined the plant cell. In 1846 he would argue that this anatomical object of the primordial utricle was made of a substance he named *"Protoplasma*."

Along with Schleiden, Carl Nägeli, Franz Unger, and Wilhelm Hofmeister, Hugo von Mohl styled himself as part of a new generation of botanists who actively sought new techniques and theoretical principles to reform botanical investigation.[30] Both von Mohl and Schleiden's styles of presentation relied botanical language that had persisted since at least the eighteenth-century, even as they were actively trying to find new ideas and terminology to replace it. This rhetorical mode was employed by their contemporaries too. On the one hand, von Mohl's 1844 essay "Some Remarks on the Structure of the Vegetable Cell" claimed to refine Schleiden and Schwann's notion of free cell formation, nothing more or less. On the other hand, it was clear to von Mohl that his attempt at refining free cell formation had instead rendered it completely implausible. In 1844 von Mohl was careful to redirect attention to the physiological role of the interior of the cell, but his arguments about the anatomical objects inside the cell were still made using a language of membranes and layers that would have been familiar to Schleiden in 1838.

Von Mohl initially framed his 1844 essay as a modification of Schleiden's theory of free cell formation, and two-thirds of "Remarks on the Structure of the Vegetable Cell" reads as a friendly critique of a recent examination of tree-bark cells undertaken by yet another botanist, Theodor Hartig (1805–1880).[31] Whereas Schleiden and Schwann argued that cell multiplication involved

29. Gerald L. Geison, "The Protoplasmic Theory of Life," 274.

30. Julius Sachs, *History of Botany (1530-1860)*, trans. Henry E. F. Garnsey (Oxford: Clarendon Press, 1890), 171–72.

31. Hugo von Mohl, "On the Structure of the Vegetable Cell," trans. Arthur Henfrey, *Taylor's Scientific Memoirs* 4 (1846): 91–114. The original German text was spread over several issues of von Mohl's own weekly, *Botanische Zeitung*.

layers of membrane being condensed by the agency of the nucleus, von Mohl suggested that this membrane was a transient *Primordialschlauch*, or "primordial utricle," a sac-shaped body that always seemed to accompany the appearance of the nucleus of young cells.[32] This comformed with work being done by other botanists who were also trying to refine or give more detail to Schleiden and Schwann's relatively simple claims about cellular anatomy, and who were showing that the essential features of the cell comprised more than just a membrane and a nucleus. "The question now arises," von Mohl wrote,

> whether the primordial utricle is to be regarded as a cellular membrane (*Zellhaut*), or whether it is not rather to be reckoned among the contents of the cell and looked upon as a coagulated mucilaginous coating on the cellular membrane, for which indeed it has certainly been frequently taken…The substance of which the primordial utricle is constituted appears to be, if not identical, at least nearly allied to the muco-granular substance which usually invests the nucleus as an irregular mass.[33]

On the surface, whether the primordial utricle was a "membrane" or part of "the contents of the cell" seems to be a trifling distinction, and the apparent narrowness of von Mohl's claim seemed to be echoed by the statement that he was "on the whole…confirmatory of Schleiden's theory respecting the formation of cells."[34] Such statements obscured his genuinely novel strategy for explaining cell growth. Although the scientific problem of cell formation remained the same as it had been in 1838, in 1844 von Mohl was shifting the material locus of the problem to the primordial utricle, an organ. In Lakoff and Johnson's categorization of ontological types, the primordial utricle was an *object* within the cell that he called a *Schlauch*, a utricle or sac, rather than a layer, a *Membran* or *Schicht*:

Hugo von Mohl, "Einige Bemerkungen über den Bau der vegetabilischen Zelle," *Botanische Zeitung* 2, nos. 15–19 (1844): 273–77, 289–94, 305–10, 321–26, 337–42.

32. *Schlauch* could also be translated as "sleeve" or tube, or perhaps "layer" (although "layer" is more accurately rendered as "*Schicht*." The English use of the word "utricle" refers to a sac or bladder-shaped body; "Utricule, *n.*1," *OED Online* (Oxford University Press), accessed 5/16/16, http://oed.com/view/Entry/220800.

33. Hugo von Mohl, "On the Structure of the Vegetable Cell," 99; in the German 293–94. The original reads: "Es ensteht nun die Frage, soll man den Primordialshclauch als eine Zellhaut betrachten, oder soll man ihn nicht vielmehr zum Zelleninhalt rechnen und soll man ihn nicht als einen geronnen, schleimigen Ueberzug der Zellhaut ansehen, wofür er gewiss schon häufig gehalten wurde…Es scheint die Substanz, aus welcher der Primordialschlauch besteht, mit der schleimigkörnigen Substanz, welche meistens den Nucleus in Form einer unregelmässigen Masse umhüllt…"

34. *ibid.,* 97, in the German 291.

the primordial utricle had to be seen as a blobby mass or at least a kind of congealed envelope, not simply a boundary. As a kind of mass, the primordial utricle had texture, being "congealed" and "slimy" ("*geronnen, schleimig*"), qualities that a boundary would not have.

After having made the distinction between membranes and the primordial utricle, the bulk of the 1844 article was a critique of the Prussian botanist Theodor Hartig, and an object that Hartig called the *ptychode*, or "a third inner membrane" ("*eine dritte, innere Haut*").[35] The majority of the 1844 article's text and images were devoted to this rather technical debate. If any given plant cell is treated with a diluted acid — von Mohl mentions nitric, hydrochloric, and sulfuric acids — and then stained with iodine, then several layers appear to separate off from the outer boundary of the cell.[36] For Hartig, as was the case for Schleiden and Schwann, this was evidence that the primary, outermost layer of mature cells (especially lignified, or woody cells) was deposited by a secondary membrane, which itself was deposited by the ptychode or tertiary membrane, such that the thick primary membrane is actually the youngest; the inner membrane, according to von Mohl's gloss, was distinguishable by its different coloration (staining darker yellow) when treated with sulphuric acid and stained by iodine. Hartig saw cells growing from the center outwards, through a layering of membranes in concentric rings, which von Mohl thought had no grounding in the "mechanical conditions" that were visible under the microscope.

Von Mohl illustrated these "mechanical conditions" with thirty-four figures (Figure 1.1). The engravings are remarkably schematic and didactic, drawn simply in order to demonstrate the force of his argument.[37] The first figures show the primordial utricle completely separated from the primary

35. *ibid.,* 101–102; in the German 307.

36. Von Mohl discusses both an initial application of acid followed by iodine staining, and an initial iodine stain followed by fixation by acid. The latter is for the purpose of highlighting the primordial utricle, the former for showing the separation of layers of the outer membranes.

37. Of von Mohl's relatively sparse illustrative practices, Julius Sachs suggested that "von Mohl's microscopic drawings do not aim at giving the collective impression, but at facilitating the understanding of the delicate structure of single cells

membrane, to demonstrate its existence as an independent anatomical object; the artificially coagulated primordial utricle, colored pale orange, is isolated and exaggerated, shown both completely and partially separated from the walls/membrane (Figure 1.2). Using a gentler acid treatment, however, von Mohl reported seeing what he referred to as "secondary membranes" curve and terminate, rather than form even, concentric or parallel layers (Figures 1.3 and 1.4).[38] "The layers of the secondary membrane do not run parallel to the outer walls of the cell, but exhibit an arched curve directed towards the interior of the cell."[39] The primordial utricle would still adhere to the primary membrane. Von Mohl inferred this from examining a structure that he confusingly referred to (and confusingly translated) once as "canals of pores" ("*Porenkanäle*") and elsewhere as "canals of dots" ("*Tüpfelkanäle*") in a long discussion of the structure of woody cells (Figure 1.5). These pore canals would not be apparent in their natural state, von Mohl argued, but applying hydrochloric acid would reveal their cleft, finger-like structure, "split into many lamellae," left over at the point at which the primordial utricle was once attached, before the woody cell fully matured.[40]

Through all of his diagrams, von Mohl assertively argues that, with exception of the outermost, primary membrane, the inner "membranes" were not continuous borders or layers of deposits. For von Mohl, the only "mechanical" explanation was that the outer parts of the cell

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and their combination by aid of the simplest possible lines. He always despised pictures from the microscope…a kind of artistic restorations of the originals and to some extent a playing with science; and in his later publications he was more sparing of illustrations or omitted them altogether, in proportion as he acquired the power of giving clear verbal explanations of even difficult structural conditions." Julius von Sachs, *History of Botany (1530-1860)*, 298.

38. Biologists in the nineteenth century studied a wide and eclectic range of species in their laboratory research, since lab and microscopic studies were still seen as closely allied to (or at least haunted by) natural history and systematics; see Frederick B. Churchill, "Life before Model Systems: General Zoology at August Weismann's Institute," *American Zoologist* 37, no. 3 (1997): 260–68. For example, von Mohl published not infrequently on systematics and plant biogeography, despite his predominant interest in anatomy and development; see his obituary and bibliography by Anton de Bary, in "Hugo von Mohl," *Botanische Zeitung* 30, no. 31 (1872): 561–80.

39. Hugo von Mohl, "On the Structure of the Vegetable Cell," 106; in the German 323.

40. *ibid.,* 109; in the German 324–25. "Canals of pores" ("*Porenkanäle*") appears on 102; in the German 307. "Canals of dots" ("*Tüpfelkanäle*") appears on 108–10 and 114; in the German 324–26, and 341.

thickened as the primordial utricle retreated inward, while the primordial utricle remained anchored to the primary membrane. Whereas Hartig (and Schleiden and Schwann) held that the nucleus created ever-thicker layers of cell, building from the nucleus outward, von Mohl argued, on the basis of observing cells swelled by acid treatments, that the primordial utricle was responsible instead for creating the outermost membranes or walls of cells first, before retreating inward, depositing successive layers of secondary membrane. By arguing that the agent of cellular growth worked from the edges of the cell towards the middle, von Mohl thus reversed Schleiden and Schwann's carefully wrought arguments about growth by intussusception or juxtaposition; in fact von Mohl avoided the latinate terms altogether. And although he was not certain of it, von Mohl thought that primordial utricles reproduced either by being absorbed by the cell, after which the cell produced two more utricles; or that the original primordial utricle constricted into two, in a process akin to cell division.[41]

Von Mohl then rather excitedly speculated, first, that the cell wall might be formed through a chemical de-nitrogenization of the primordial utricle(s), and second, that cells became divided when two primordial utricles deposited a septum between themselves.

> The fact that the substance of the primordial utricle is entirely distinct from the substance of the permanent cell-wall, as shown by its dark colour with iodine and its insolubility in acid, is clearly of the highest consequence. If the former circumstance might be regarded, as some French chemists maintain, as an evidence of the presence of nitrogen in an organized body, the primordial utricle would either consist of, or be thoroughly imbued with, a nitrogenous substance, and during its existence, the cell-wall structure would be entirely free from nitrogenous combinations, since this is seldom, and then but feebly coloured yellow by iodine during that period.[42]

This purely hypothetical statement was not supported by any visual witnessing of the *process* of cell wall formation, nor (as von Mohl would admit two years later) was the primordial utricle known to

41. *ibid.,* 96; in the German 290. Von Mohl had made a case for cell division in 1837 in filamentous algae: Hugo von Mohl, "Ueber die Vermehrung der Pflanzen-Zellen durch Theilung," *Flora oder allgemeine botanische Zeitung* 20, no. 1 (1837): 1–32.

42. Hugo von Mohl, "On the Structure of the Vegetable Cell," 100; in the German 305.

have significantly more nitrogen than the relatively nitrogen-free cell wall. Visually, the only evidence von Mohl could point to was that cells stained with iodine "which have remained for a number of years in spirit," or more conveniently fixed with nitric or hydrochloric acid, showed "a completely closed, thin-walled, cell-like vesicle" ("*eine vollständig geschlossene, dünnwandige zellenähnliche Blase*"). He was more intrigued by the physiological possibilities of giving more agency to the contents of the cell, even if at the expense of considerations of the membrane or nucleus, which Schleiden and Schwann had emphasized. In addition to his speculation about the de-nitrogenization of the primordial utricle, von Mohl noted that the lifecycle of the primordial utricle pointed to key features of cellular physiology: since older cells lack the primordial utricle, the latter structure was not essential for all aspects of the plant cell's life. "Although both the origin and the growth of the cell are dependent upon it, the physiological functions of the cell are not at all connected with the primordial utricle," von Mohl decided, noting that the most mature layers of tree bark lack the primordial utricle. Then again, switching into a more colloquial form of speech,

> Ought we not then to conclude that the primordial utricle takes a part in the assimilation of the crude nutritive juices, as well as in the origination of the cell? But enough of conjectures as to the functions of an organ whose very existence has yet to be admitted by other observers![43]

Was it possible that the primordial utricle was the active agent of the plant cell, the organ responsible for growth, digestion, and assimilation? Von Mohl allowed his excitement to announce itself on paper, but he was still concerned with demonstrating the *anatomical* possibility that the primordial utricle existed in the first place. Yet, within the space of a paragraph, we can see von Mohl's relative conservativism in regard to the important defining characteristic of the cell — the wall or membrane — contrasted with the physiological possibilities that an evolving and dissolving primordial utricle could suggest.

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43. *ibid.,* 101; in the German 306.

Within two years von Mohl began to believe that he needed a different kind of vocabulary, and along with it a different kind of materialism — and out of this different materialism the concept of *Protoplasma* was created. Unlike his 1844 essay, von Mohl's 1846 essay "Ueber die Saftbewegung im Innern der Zellen" did not focus on membrane formation or cellular genesis.[44] Freeing himself from most obligations to the outer boundary of the cell, von Mohl rethought the relationship between the nucleus, the primordial utricle, and the sap (*Saft*) of the cell, by paying closer attention to the composition of various substances of the cell and some of their more tactile characteristics. Intrigued by the fact that both the nucleus and a "viscous, colorless mass, mixed with minute granules" ("*eine zähflüssige, mit feinen Körnchen gemengte, ungefärbte Masse*") formed prior to the appearance of either a new nucleus or new primordial utricle, von Mohl began to entertain the notion that the nucleus and the primordial utricle shared an origin.[45] This viscous mass "furnishes the material for both the formation of the nucleus and primordial utricle," a fact both immediately visible under the microscope and proven by the fact that they "react towards iodine in an analogous manner," suggesting a similar nitrogenous composition.[46] Von Mohl thus endowed this viscous fluid with the powers of creating both the nucleus and the cell membrane, and "since…their organization is the process which induces the formation of the new cell, I trust it will be considered justifiable if I propose to designate this substance by the word *Protoplasma*, a term which recalls to mind its physiological function."[47]

Although historians and von Mohl's contemporaries alike have thought that von Mohl's new term *Protoplasma* was a synonym for the *Primordialschlauch*, von Mohl himself was not so sure of it.

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44. Hugo von Mohl, "Ueber die Saftbewegung im Innern der Zellen," *Botanische Zeitung* 4, nos. 5–6 (1846): 73–78, 89–94. For the English translation, likely also done by Arthur Henfry: Hugo von Mohl, "On the Circulation of the Sap in the Interior of Cells," *Annals and Magazine of Natural History* 18 (July 1846): 1–10.

45. Hugo von Mohl, "On the Circulation of the Sap in the Interior of Cells," 2; in the German 73.

46. *ibid.,* 3; in the German 74.

47. *ibid.,* 3; in the German 75.

The primordial utricle was made of protoplasm, or so von Mohl continued to argue well into the 1850s. In a short textbook, first published in English in 1852 (and in German later in 1853), von Mohl protested that Carl Nägeli and others had mistaken the primordial utricle as a structureless "layer of mucilage," whereas he insisted that the primordial utricle as an anatomical object: "it certainly must be regarded as a membrane and not a layer of fluid mucilage."[48] Having spent so much time in the 1840s arguing that the primordial utricle was not a membrane, this must have been genuinely confusing to von Mohl's colleagues. Yet for von Mohl, this was consistent with the way he had defined the primordial utricle as an object, and protoplasm as a specific substance that made up the primordial utricle; he may as well have invented a term like *"Primordialschlauchstoff,"* had he been so inclined. When the slightly younger Berlin botanist Nathanael Pringsheim (1823–1894) suggested in 1854 that the term protoplasm simply replace the primordial utricle, von Mohl strenuously objected, insisting that there was a reason that he made the distinction between the organ and the substance from which it was made: von Mohl did not actually claim to know what the constitution of protoplasm was.

> With this term I designated a particular *anatomical* part of plants, independent of its chemical composition, which is still not yet accurately known; under no circumstance did I want to coin a collective name for the protein substances, which are present in the most diverse anatomical proportions, and which shall be named by the chemists, who are studying them in far greater detail. To employ the term protoplasma as an overall designation of the plant proteins, of legumins, diastases, etc., is as useful as to subsume animal fibers, casein, etc. all under the term "blood."[49]

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48. Hugo von Mohl, *Principles of the Anatomy and Physiology of the Vegetable Cell*, trans. Arthur Henfrey (London,: J. Van Voorst, 1852), 37. In the introduction to the English version, von Mohl noted that he originally completed this overview work in 1850, but the German was only published in 1853 as a chapter, "Die vegetabilische Zelle," in Rudolph Wagner's *Handwörterbuch der Physiologie mit Rücksicht auf physiologische Pathologie*, Bd. 4 (Braunschweig: Friedrisch, Bieweg und Sohn, 1853), 167–310. See 199–200, there the passage cited reads, "ist doch gewiß für eine Haut und nicht für eine Schichte flüssigen Schleims zu erklären."

49. Hugo von Mohl, "Der Primordialschlauch," *Botanische Zeitung* 13, no. 40–42 (1855): 689–701, 713–25, 729–37, on 690ff. "Ich bezeichnete damit bestimmten *anatomischen* Bestandtheil der Pflanze, ganz abgesehen von seiner chemischen, bis jetzt überhaupt nichts weniger als genau bekannten Zusammensetzung, keineswegs aber wollte ich damit einen Collectivnamen für die Proteinsubstanzen geben, welche in den verschiedensten anatomischen Verhältnissen vorkommen und für welche eine neue Bezeichnung aufzustellen wir den Chemikern, welche dieselbe schon näher studiren werden, ruhig überlassen können. Den Ausdruck Protoplasma zur Gesamtbezeichnung des vegetabilischen Eiweisses, des Legumins, der Diastase u.s.w. zu verwenden, ist gerade so zweckmässig, als wenn man den thierischen Faserstoff, Käsestoff, u.s.w. unter dem Ausdrucke Blut zusammen wollte."

For von Mohl, to lump *all* of the nitrogenous constituents of the plant cell under *Protoplasma* or even *Schleim* was to relinquish the original functional-anatomical insight, that this substance was specifically associated with the genesis of the cell nucleus and the primordial utricle, object that created the primary cell membrane. It certainly did not help that in 1852 he had called the primordial utricle a "membrane," whereas in the 1840s he had spent so much time arguing precisely the opposite.

Von Mohl's confusion or reversal of opinion in the 1850s as to whether the primordial utricle was or was not a "membrane" likely stemmed from the transformation of what the term "membrane" meant, and what its ontological status was. When von Mohl initially engaged with Hartig and Schleiden, the cell membrane was, ontologically, a *container*, in the sense given by Lakoff and Johnson: it was the boundary that defined the cell, in relation to other cells. When von Mohl began to argue first that the primordial utricle was among the contents, then an organ, then a membrane within the cell, the primordial utricle had subtly transformed into a more definite *object*, one with a distinct identity among other objects or parts within the cell. Thinking of the cells in terms of functional anatomy did not require von Mohl to think about the composition of those cellular parts. The shift to thinking of protoplasm more clearly as a substance would require an intervention from other disciplines with very different aims and interests.

c. *Sarcode and Protoplasm*

Von Mohl gave protoplasm six morphological features in "Ueber die Saftbewegung" in 1846: it was viscous, it contained granules, it was nitrogenous in a way that the wall or membrane were not, it had the power to create vacuoles, it did not mix with other less viscous fluids, and, most importantly, it exhibited an irregular flow or circulation. It was the last three that eventually became

the crucial points of synthesis that provided a way of seeing the contents of plant and animal cells as essentially the same. This connection transformed *protoplasm* from a botanical term of art into the foundation of a unifying theory of physiology and a unifying theory of life. As a result, over the next two decades biologists slowly stripped away many of the more morphological connotations that von Mohl originally attached to the protoplasm in 1846.

Whereas in botany the shift in focus from the cell wall to the cell's contents was undertaken on multicellular algae and higher plants, in zoology that shift was made primarily through physiological studies of protists.[50] This meant that issues of membrane formation and the thickening of cell walls were relatively absent, with greater emphasis placed on the consistency and physiological capabilities of the substances in cells. In 1835 the French protozooligst Félix Dujardin (1801–1860) identified the *sarcode* of *Foraminifera*, a class of amoeboid protists that produce a shell or test.

> I propose to name *sarcode* that which other observers have called living jelly [*gelée vivante*], this diaphanous, glutinous substance, insoluble in water, contracting into globular masses, attaching itself to dissecting-needles and allowing itself to be drawn out like mucus; lastly, occurring in all the lower animals interposed between the other elements of structure."[51]

The textural similarities between Dujardin's sarcode and von Mohl's primordial utricle seem obvious in retrospect, but they were not seriously linked until 1850, when the botanist Ferdinand Cohn (1828–1898) forcefully claimed that "the *protoplasm* of the Botanists, and the contractile substance and *sarcode* of the Zoologists, if not identical, [then] are at all events in the highest degree analogous formations."[52] This was in part because Dujardin had been working on organisms that were not

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50. Andrew Reynolds, "Amoebae as Exemplary Cells: The Protean Nature of an Elementary Organism," *Journal of the History of Biology* 41, no. 2 (July 1, 2008): 307–37.

51. Félix Dujardin, "Recherches sur les organismes inférieurs," *Analles des Sciences Naturelles, Zoologie*, 2nd ser., 4 (1835): 343–77, 367. For a more complete history of Dujardin's sarcode concept, see E. Fauré-Fremiet, "L'oeuvre de Félix Dujardin et la notion du protoplasma," *Protoplasma* 23 (1935): 250–69. For more on Dujardin, see Gerald L. Geison, "Dujardin, Félix," in *Complete Dictionary of Scientific Biography*, vol. 4 (Detroit: Charles Scribner's Sons, 2008), 233–37, whence this translation is drawn. In the original French: "Je propose de nommer ainsi ce que d'autres observateurs ont appelé un gelée vivante, cette substance glutineuse diaphane, insoluble dans l'eau, se contractant en masses globuleuses, s'attachant aux aiguilles de dissection et se laissant étirer comme du mucus, enfin se trouvant dans tous les animaux inférieurs interposée élémens de structure."

52. Ferdinand Cohn, "Nachträge zur Naturgeschichte des Protococcus Pluvialis Kützing," *Novorum Actorum Academiae*

germane to debates in cell theory in the 1840s. Schwann based his research largely on various tissues (especially cartilage) in multicellular animals; Schleiden made note of orchids, crassula (a decorative succulent), flax lily (*Phormium*), ascomycete fungi, Mexican clover, flax, wheat and similar grasses; von Mohl's 1846 article mentioned *Chara* (a multicellular filamentous algae), spiderwort, eel grass, stinging nettle, arrowhead, pumpkin, and blackcurrant.

Dujardin's particular claims for why the sarcode might be an important feature of amoebae were largely unrelated to questions about multicellular tissue growth or structure, the topics with which cell theory would later be preoccupied. In 1835 Dujardin was more narrowly concerned with showing that what he called "vacuoles" in amoebae were not "stomachs," as his contemporary Christian Gottfried Ehrenberg (1795–1876) had claimed.[53] This was first and foremost an issue of ranking and classification. Ehrenberg wanted to understand what he called *Infusionsthierchen* as complete microscopic animals, with nervous, digestive, motor, and sexual organs. This would allow Ehrenberg to establish a firm division between plants and animals; for Ehrenberg this had the added benefit of giving even the smallest animals an irreducible complexity, foreclosing the possibility of spontaneous generation.[54] Dujardin saw them as far lower organisms, composed of little more than undifferentiated slime, and on that basis he was partisan to the view that these simple organisms were neither plant nor animal, and belonged in their own taxonomic category, *Infusoria*. Dujardin also felt compelled to show that the sarcode was not just a simple chemical, for example, albumin, gelatin, or mucus, by exposing amoebae to various chemicals and describing the effects, or lack thereof: "Its

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Caesareae Leopoldino-Carolinae Naturae Curiosorum 22 (1850): 605–764, on 644. The English version of Cohn's substantial and difficult treatise was published as a significantly shortened abstract, with several interjections by the English translator. Ferdinand Cohn, "On the Natural History of Protococcus Pluvialis," trans. George Busk, *Botanical and Physiological Memoirs of the Ray Society* 10, no. 2 (1853): 517–64.

53. For the debates between Ehrenberg and Dujardin, see Frederick B. Churchill, "The Guts of the Matter: Infusoria from Ehrenberg to Bütschli, 1838–1876," *Journal of the History of Biology* 22, no. 2 (1989): 189–213.

54. *ibid.,* 191; see also John Farley, *The Spontaneous Generation Controversy from Descartes to Oparin* (Baltimore: Johns Hopkins University Press, 1977) 55–56.

properties are distinct from those of substances with which it might have been confused because its insolubility in water distinguishes it from the albumins that coagulate in nitric acid, and at the same time its insolubility in potash distinguishes it from mucus, gelatin, etc."[55] Dujardin's sarcode was visually similar to those lower chemical substances, but it had the power to spontaneously form vacuoles, and, crucially, the power to contract.

Dujardin's sarcode concept was not unheard of outside of German and French protistology, and the term seems to have been introduced more broadly into German zoology by the Swiss-German anatomist Alexander Ecker in 1846, in a very short treatise on the contractile substance in hydras and other lower animals.[56] Ecker believed that studying hydras might illuminate the relationship between infusoria and higher animals, and he found the sarcode concept useful because it could explain hydras' immense powers of contraction and movement in the absence of any fibrillar muscle tissue. Ecker further noted that the connection between contractility in infusoria and muscle had been established by several German, French, and English zoologists and anatomists, although the term "sarcode" was not in wide circulation.[57] In 1843 Dujardin himself suggested a more general conception of sarcode in his general microscopy textbook, the *Nouveau manuel complet de l'observateur au microscope*, noting that he had found something like sarcode in mammalian genitals and in insects, lining the surface of the tracheae. In both cases he discussed a liquid with properties "*comme dans le sarcode*," referring to the substance's texture as "*mucilagineuse, diaphane et homogène*,"

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55. Félix Dujardin, "Recherches sur les organismes inférieurs," 367–68. "Ses propriétés sont donc bien distinctes de celles de substances avec lesquelles on eût pu le confondre, car son insolubilité dans l'eau le distingue de l'albumine dont il se raproche par le mode de coagulation que lui fait éprouver l'acide nitrique, et cette coagulation en mème temps que son insolubilité dans la potasse le distinguent du mucus, de la gélatine, etc."

56. Alexander Ecker, *Zur Lehre vom Bau und Leben der contractilen Substanz der niedersten Thiere* (Basel: Schweighauser'schen Univeritaets-Buchdruckerei, 1846). Ecker studied in Freiburg and Heidelberg, but held a position in physiology or anatomy in Basel from 1844 to 1850; see Friedrich von Weech, "Ecker, Alexander," *Allgemeine Deutsche Biographie* Bd. 48 (Bayerische Staatsbibliothek, 1904).

57. *ibid.,* 5. Ecker cites Focke, Franz Julius Ferdinand (J.) Meyen, Dujardin, Thomas Rymer-Jones, and Carl Theodor Ernst von Siebold.

just as he did in *Foramnifera*.[58] Dujardin even treated the microscopic investigation of plants in his textbook, where he drew a rough comparison between sarcode and the "utricular or cellular tissue" of plants. However, he insisted that the latter "have absolutely nothing in common with the cellular tissues of animals," and that plant cells' mucilaginous contents were "cambium," not sarcode.[59]

In both Ecker's and Dujardin's writings from the 1840s, we can see the interplay between epistemological and ontological concerns among mid-century biologists, and how they in fact *precluded* a quick connection between animal sarcode and plant protoplasm. Both Ecker and Dujardin were primarily interested in the sarcode concept as a designation for a specific substance with a short list of material qualities, one which was capable of a fairly specific set of vital processes. Sarcode was also a substance that was not necessarily cellular or found in cellular tissues or animals; and, for Dujardin, substances similar or analogous to sarcode were easily found with the aid of a microscope. At the same time, the prior division between plants and animals gave Dujardin pause; besides, in a didactic textbook on microscopy, an argument for the equivalence of a contractile animal substance and a vegetable substance might have been inappropriate. Unlike Schwann a few years before, Dujardin did not see himself in a position to articulate a grand, unifying theory of life: a microscope could study both animals and plants, but microscopic technique alone was apparently not enough to establish that animals and plants were fundamentally made of the same substance.

Thus the historical circumstances of Cohn's theoretical synthesis of sarcode and protoplasm suggest that a specific alignment of disciplinary interests and questions was needed for him to reach this theoretical synthesis. Cohn's "strong analogy" was made in a very long essay on "The Natural History of Protococcus Pluviais," published in the prestigious annual journal of the Leopoldina

58. Félix Dujardin, *Nouveau manuel complet de l'observateur au microscope* (Roret, 1843), 131, 141.

59. *ibid.,* 168.

(Figure 1.6).[60] *Protococcus pluvialis* (now also known as *Haematococcus*) is a species of unicellular green algae, and Cohn's natural history of the organism was one of the more important pieces of his program for microscopic cryptogamic botany.[61] *Protococcus* has a complicated life cycle, and one of Cohn's primary goals in the essay was to argue that what prior investigators thought were ten different species were, in fact, only ten different forms of one species, *Protococcus pluvialis*.[62] Cohn believed that examining the anatomy and physiology of *Protococcus* could not only clarify its taxonomic identity, but also say something important about the essential difference between plants and animals. Because some of *P. pluvialis*' forms were motile, Cohn argued that the traditional division of sessile plants and motile animals was too crude to provide a basis for classifying what he believed to be one species. Carefully following *Protococcus* across several seasons and in different freshwater environments, Cohn reported that the organism in question displayed different morphological features depending on its immediate physiological needs: it became green when its vegetative powers were needed, and turned bright red in preparation to fructify.[63] The organism became motile or sessile depending on light and temperature, and it could even have a stronger or more gelatinous cell membrane, though Cohn was unspecific on its physiological importance.[64]

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60. See note 52, above.

61. Cohn argued that *Protococcus pluvialis* was a unicellular *plant* ("*eine einzellige Pflanze*"), with a motile form and a sessile form, and not merely a unicellular alga: Cohn argued that only plants went through a genuine alternation of generations, but others (including the English reviewer) did not accept this claim. Still others had suggested that certain stages of *P. pluvialis*' life cycle were multicellular, but Cohn wanted to demonstrate that an alternation of generations was possible with a strictly unicellular organism. Ferdinand Cohn, "On the Natural History of Protococcus," 523–524. For more on Cohn's broader approach to biology and medicine, see Christina Matta, "The Science of Small Things: The Botanical Context of German Bacteriology, 1830–1920" (Ph.D. dissertation, University of Wisconsin-Madison, 2007), 89–90.

62. Ferdinand Cohn, "On the Natural History of Protococcus Pluvialis," 559–60; in the German 749–50. The species Cohn wanted to unite into one included: *Protococcus coccoma, P. pulchur, P. minor, Gyges granulum, P. turgides,* "perhaps" *P. versatilis, Gyges bipartitus, P. dimidiatus,* some varieties of *Gonium, Pandorina Morum, Botryocystis Volvox,* and members of either *Uvella* or *Syncrypta, Microhaloa protogenita,* some form of *Euglenae, Astasia,* and *Bodo*. Cohn found this situation intolerable, "a state of complete anarchy in the domain of microscopic organisms."

63. *ibid.,* 519; in the German 611.

64. *ibid.,* 520; in the German 620–21.

Having argued that all of these forms were one organism, Cohn then sought to dramatically redefine the boundary between the plant and animal kingdoms, and it was to this end that Cohn brought together Dujardin's sarcode and von Mohl's protoplasm. Cohn began by reviewing the fundamental similarities between the two: both sarcode and protoplasm were recognized to be contractile; various authors had noted (albeit inconsistently) that they could generate vacuoles; and they both possessed similar appearance and texture (and reacted similarly to stains and fixatives). Then, with great flourish, Cohn directly attacked the traditional basis for the division between plants and animals that had prevailed since Aristotle:

> *It is not the animal organism itself which is contractile, but only a single tissue in it*; all the rest, skin, bones, connective tissue, etc., are as rigid as the vegetable membrane, or at most elastic; in the higher animals only the muscles are contractile, and only in the lowest, namely the Infusoria, is the entire body contractile.[65]

Thus Cohn sought to redefine plants and animals on the basis of the location of motion and contraction within the organism — and if the organism was very basic or unicellular, then its taxonomic status was based on the location of the protoplasm within the cell.

> Whence, the distinction between animals and plants, viewed in the above light, must be thus understood; that in the latter, the contractile substance, as the primordial utricle, is enclosed within a rigid, ligneous membrane, which permits only an internal motion, evidenced in the phenomena of circulation and rotation; while in the former it is not thus enclosed. The protoplasm, in the form of the primordial utricle, is, as it were, the animal element in the plant, in which it is *confined,* being *free* only in the Animal kingdom.[66]

For Cohn, it was thus completely within reason to think of *Protococcus* as a motile plant, because its motion was generated by the protoplasm from within a more-or-less rigid membrane. It did not reach out into the world with pseudopodia like an amoeba, but rather swam towards light to take advantage of its vegetable powers. By collapsing the distinction between plant protoplasm and

65. *ibid.,* 533; in the German 662.

66. *ibid.,* 535; in the German 664–65. The original German is: "Demnach müsste der Unterschied zwischen Theiren und Pflanzen von obigem Gesichtspuncte aus so gefasst werden, dass bei diesen die contractile Substanz, als Primordialschlauch, innerhalb einer starren Holzfasermembran eingeschlossen ist, welche ihr nur eine innere, normal sich in den Phenomen der Circulation und Rotation aussprechende Beweglichkeit getstattet — bei jenen aber nicht. Das Protoplasma in der Form des Primordialschlauchs ist gleichsam das thierische Element in der Pflanze, das hier noch gebunden ist und erst im Thierreiche frei wird."

animal/infusoria sarcode into a single, unitary protoplasm, Cohn also reinforced a physiological and anatomical division between plants and animals. *Protococcus*, and its many generations and forms, was a plant.

And yet, despite Cohn's impressive synthesis and his very thorough attempt to reshape both biology and natural history, in the next decade protoplasm theory became detached from Cohn's subtle analysis of the relationship between cellular anatomy and the taxonomic unity of life. Through the 1850s the tie between the physiological phenomenon of contractility and an ill-defined nitrogenous substance rapidly gained currency, such that by the 1860s protoplasm itself became the unifying theory of life. In the early 1860s, the Bonn anatomist Max Schultze (1825–1874) argued for yet another round of terminological reforms, abandoning not only the older terms "sarcode" and "primordial utricle," which were still in use, but making a move towards abandoning the idea of the cell entirely. In 1861 Schultze published the provocatively-titled "On Muscle Corpuscles and That Which Has Been Called a Cell," in which he declared: "A cell is a clump of protoplasm, in the interior of which lies a nucleus" ("*Eine Zelle ist ein Klümpchen Protoplasma, in dessen Innerem ein Kern liegt*").[67] This was the first of several statements in which Schultze claimed that, generally speaking, the membrane is unneccessary in many kinds of cellular life, and that the proper morphological definition of the cell was limited to the protoplasm (the contractile substance) and the nucleus — completely disregarding Cohn's definition of the plant cell as being essentially bounded and confined.

As Andrew Reynolds has argued, Schultze's redefinition of the cell was premised on the amorphous nature of the amoebae that Schultze studied, and the amoeba became "exemplary" of both cells and of organisms precisely for this lack of form. For Schultze and many others, amoebae

67. Max Schultze, "Ueber Muskel-körperchen und das, was man eine Zelle zu nennen habe," Müllers *Archiv für Anatomie, Physiologie, und wissenschaftliche Medezin*, 1861, 1–27, on 11.

were life at its simplest: amoebae, and by extension "formless" protoplasm became widely seen as possessing all of the necessary phenomena of life, as well as resting at the bottom of the evolutionary tree or chain of being.[68] By itself, Schultze argued, protoplasm was capable of changing shape, performing autonomous movement, nourishing itself, even merging with other materials in order to create the rest of a larger organism; anything else around or embedded in the protoplasm existed only in service to the protoplasm's unique activity.[69] Stripped of form, the most basic cell — and therefore the most basic unit of life — became nothing more than a mass or unit of a substance endowed with basic vital functions.

The ontological status of protoplasm as a substance was thus established through its connection to the interest in studying amoebae as cellular organisms, and through the specific history of the sarcode as an idea generated from Dujardin's study of *Foraminifera* amoebae. As Reynolds puts it, "It was through protoplasm's new status as the *Urstoff* of life that amoebae could be seen as exemplary of cells (and of life) in general."[70] As we have seen in protoplasm's history in the 1840s and '50s, the amoeba's exemplary status was not yet an obvious proposition, because the protoplasm was so closely tied to cell theory, and cell theory was at once very much a morphological *and* physiological theory. Only the sarcode concept had such an amorphous quality, having originated in Dujardin's description of amoebae. By denying the necessity of the cell membrane, Schultze had brought to completion an effort to shift biologists' attention to the material basis of the cell, and away from Schleiden and Schwann's prioritization of the cell's nature as a boundary membrane that enclosed a nucleus. The distillation of the cell down to a single substance would have been novel to Dujardin, lacking in interest to Cohn, and patently incorrect to von Mohl: in each of

68. Andrew Reynolds, "Amoebae as Exemplary Cells," 317.

69. Max Schultze, "Ueber Muskel-körperchen," 17.

70. Andrew Reynolds, "Amoebae as Exemplary Cells," 317.

their own contexts, the protoplasm concept was merely useful for fulfilling other agendas. Yet, as they sought to refine or create new ideas in taxonomy, anatomy, and physiology, Dujardin, von Mohl, and Cohn were all investing more and more importance in this slimy, viscous substance, one which had nearly been an afterthought in cell theory in 1839.

d. Conclusion: Protoplasm as the "Physical Basis of Life"

Schultze had made protoplasm the center of a reformed cell theory, but in 1868 T.H. Huxley (1825-1895) rendered it into a complete theory of life itself.[71] Already a great celebrity in Britain, in 1868 Huxley delivered a lecture, "On the Physical Basis of Life," on Sunday, the 8th of November, 1868 in Edinburgh, on the invitation of a Rev. J. Cranbrook. "On the Physical Basis of Life" generated a tremendous popular and scientific response of the sort most biologists could only imagine, and it was reprinted widely in Britain, the United States, and even Australia.[72] The lecture itself was mostly devoted to issues of theology and philosophy, but at its heart Huxley wanted to establish that "a threefold unity — namely a unity of power or faculty, a unity of form, and a unity of substantial composition — does pervade the whole living world," and that all three aspects were grounded in the protoplasm.[73] Huxley had been attentive to Cohn and Schultze's writings in Germany, and many of the technical elements of "On the Physical Basis of Life" relied on their discussions and definitions of protoplasm.[74] However, Huxley was not interested in debating the

71. Gerald L. Geison, "The Protoplasmic Theory of Life."

72. See Barry W. Butcher, "Darwin Down Under: Science, Religion, and Evolution in Australia," in *Disseminating Darwinism: The Role of Place, Race, Religion, and Gender* (Cambridge: Cambridge University Press, 1999), 39–60. "On the Physical Basis of Life" was first printed in *The Fortnightly Review* in February 1869 in Britain, and in the New York tabloid *The World* the same month, (see Gerald L. Geison, "The Protoplasmic Theory of Life," 279); apparently demand for the lecture in Britain was so great that the issue of *The Fortnightly Review* was reprinted in four additional editions.

73. T. H. Huxley, "On the Physical Basis of Life," *The Fortnightly Review* n.s., 5 (1869): 129–45, on 130.

74. Gerald L. Geison, "The Protoplasmic Theory of Life," 273.

finer points of cell theory: he wanted to defend scientism against theology, positivism, and philosophical materialism, and also defend a materialist theory of life against so-called vitalists.[75] Huxley, then, could be free to discuss the circulation of protoplasm, its contractile power, its ability to absorb nutrients and transform them into more protoplasm. He was relatively silent on problems of cell structure, growth, and taxonomy, and poured all of his rhetorical energy into protoplasm's "substantial composition" and physiology. Thus Huxley could say, and Schultze or Cohn could not, "Carbon, hydrogen, oxygen, and nitrogen are all lifeless bodies.…But when they are brought together, under certain conditions they give rise to [a] more complex body, protoplasm, and this protoplasm exhibits the phenomena of life."[76]

The transformations of the cell into a formless substance, the protoplasm, could be seen as a series of theoretical reductions of vital phenomena to smaller and smaller parts, a part of the long history of reductionism, attacks against vitalism, and a triumphal march toward mechanistic and materialist approaches to life. What this history of the cell and protoplasm shows instead, however, is that these kinds of major conceptual changes are often tied to other, more immediate, and often more diverse agendas. One of the advantages of Lakoff and Johnson's distinction between ontological metaphors of container, object, and substance, is that it allows very similar terms to speak to different purposes. The specific contexts in which it might be useful to speak of organisms as being "made of protoplasm" (*e.g.,* claims about the unity of life, or material basis of vital phenomena) versus organisms "divided into cells/lumps of protoplasm" (*e.g.,* comparing the anatomy of jellyfish to slime molds) are analogous to the specific contexts in which it might be useful to distinguish between discussions of water resources versus the health or supply of a specific body of water. The protoplasm

75. Gerald L. Geison, "The Protoplasmic Theory of Life," 285–292. Huxley had other critiques of German cell theory; see Marsha L. Richmond, "T. H. Huxley's Criticism of German Cell Theory: An Epigenetic and Physiological Interpretation of Cell Structure," *Journal of the History of Biology* 33, no. 2 (2000): 247–89.

76. T. H. Huxley, "On the Physical Basis of Life," 135.

concept as a specific, active part of the cell was useful to von Mohl and Cohn in ways that it would not be to Schultze and Huxley. Huxley was one of the only scientists in the early history of the protoplasm concept to make grand claims about protoplasm as the "physical basis of life," and as Geison and Strick have shown, his concerns were themselves unique to his role as a scientist in the public eye.

Thus it was not only possible, but historically reasonable for both the protoplasm and cell theories to coexist, despite overlaps and incongruities between the two. By expressing different ontologies of life, the words "cell" and "protoplasm" were each useful in different kinds of investigation: the former focused on identifying anatomical objects in the cell, such as chromosomes and chloroplasts, the latter focused on the material nature and structure of protoplasm as a whole. These overlaps and incongruities could, on the one hand, lead E. B. Wilson to insist that the cell was nothing more than a "mass of protoplasm containing a nucleus"; and on the other hand, lead Julius Sachs to argue that protoplasm theory had supplanted and surpassed the original insight provided by Schleiden and Schwann's cell theory.[77]

The history discussed in the rest of this dissertation will only occasionally touch on the history of the cell's anatomy: the proof of the existence and function of the mitochondria, Golgi bodies, chromosomes, etc. Hugo von Mohl's research in the 1840s and '50s, identifying objects like the *Primordialschlauch*, was within, or even one of the origin points of this long tradition of cellular anatomy. Protoplasm research was a very different kind of endeavor. Because protoplasm was so amorphous, different ontological and epistemological frameworks were needed to understand why its physiological vitality could arise from such an unstructured substance. These questions about the material structure or composition of protoplasm in relation to physiological function would orient

77. See Andrew Reynolds, "The Redoubtable Cell," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 41, no. 3 (September 2010): 194–201.

later biologists around theories of matter in physics and chemistry in ways that cellular anatomy would not.

Chapter 2: The Structure of Protoplasm and Fixation Artifacts, 1882–1899

> It can make me uncomfortable to think that any micrograph gives us even a remotely complete picture of the structure of cells, and when it is said: 'the cell membrane is structureless, the protoplasm is a homogenous mass,' etc., this should probably only be taken to mean: the cell membrane *appears* to us to be structureless, the protoplasm *appears* to us as a homogenous mass.
>
> —Ernst von Brücke, *Die Elementarorganismen*, 1861[1]

In 1882 Walther Flemming (1843-1905) published an instant classic of German cell research, his monograph *Zellsubstanz, Kern, und Zelltheilung*. Flemming's book was famous for giving one of the first detailed descriptions of mitosis and of the carefully choreographed multiplication and division of the chromosomes during cell division. Yet, mitosis was not the only topic for which the book would be known. In subsequent years a single experiment, breezily mentioned in a footnote on page 51, would be cited time and again as a watershed moment in the history of cell and protoplasm theory (Figure 2.1):

> Incidentally, osmic acid of 1–2% concentration produces protoplasmic stands and nuclei in *Spirogyra* and other plant cells that are not as true to nature as the other reagents mentioned above; namely, the nuclei are often shrunk in the osmium preparation.[2]

Questions about microscopic artifacts were not new in the 1880s, and this offhand comment did not seem to attract much attention in the immediate aftermath.[3] However, beginning in 1886 Flemming's casual observation of a structure caused by osmic acid that was "not as true to nature" would be exhumed and cited by biologists repeatedly over the next two decades as having

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1. Ernst von Brücke, "Die Elementarorganismen," in *Pflanzenphysiologische Abhandlungen von Ernst von Brücke*, ed. Alfred Fischer, Ostwald's Klassiker Der Exakten Wissenschaften Bd. 95 (Leipzig: Wilhelm Engelmann, 1898), 54–79, on 58, emphasis added.

2. Walther Flemming, *Zellsubstanz, Kern und Zelltheilung* (Leipzig: F. C. W. Vogel, 1882), 51.

3. On the history of microscopy and microscopic fallacies earlier in the nineteenth century, see Jutta Schickore, *The Microscope and the Eye: A History of Reflections, 1740-1870* (Chicago: University of Chicago Press, 2007).

inaugurated a major crisis in modern microscopic technique. This crisis would push cytologists to reform and better understand their techniques for specimen preparation and preservation. Yet doing so had an unexpected consequence for the search for the structure of living protoplasm: by the end of the nineteenth century, cytologists were using simple, non-living preparations of gelatin, protein solutions, and other simple colloidal materials as a stand-in for real living cells.

The search for a clear anatomical structure to protoplasm had its origins in 1861, when the physiologist Ernst von Brücke (1819–1892) famously argued that the cell and protoplasm must have a structure and organization that could account for its own complex life processes as a fully independent organism.[4] Citing Max Schultze's redefinition of the cell as a "lump of protoplasm containing a nucleus," von Brücke argued that protoplasm could not be thought of as a "homogenous mass" and still explain the manifold diversity of vital phenomena: protoplasm's vitality had come from some kind of anatomical structure, analogous to the way that living organisms possess organs and tissues to perform different physiological functions. Any scientific or ideological usefulness of understanding protoplasm as a formless or undifferentiated living substance conflicted with existing conceptual and institutional structures in biology that tended to privilege cellular anatomy and the identification of parts of the organismal whole.[5] Unfortunately, protoplasm in its natural state was a colorless, transparent, slightly viscous mass — qualities that thwarted Brücke's and everyone else's desire to see a clear and distinct anatomical structure within it.

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4. Brücke and "Die Elementarorganismen" have been favorites of historians of cell theory, often cited as the biologist who hardened the consensus that a cell is a whole and elementary organism. For a small sample of see: Andrew Reynolds, "The Redoubtable Cell," *Studies in History and Philosophy of Biological and Biomedical Sciences* 41, no. 3 (September 2010): 194–201; Hans-Jörg Rheinberger, "Zum Organismusbild der Physiologie im 19. Jahrhundert: Johannes Müller, Ernst Brücke, Claude Bernard," *Medizinhistorisches Journal* 22, no. 4 (1987): 342–51; François Duchesneau, "Cytoplasmic Individuality: The Cell as Elementary Organism" (ISHPSSB conference talk, Montréal, 2015); Frederic L. Holmes, "The Milieu Intérieur and the Cell Theory," *Bulletin of the History of Medicine* 37 (1963): 315–35.

5. On the changes cellular and microscopic anatomy brought to anatomy as a whole, see Lynn K. Nyhart, *Biology Takes Form: Animal Morphology and the German Universities, 1800-1900* (Chicago: University of Chicago Press, 1995), 80–90.

Beginning in the mid-1880s, biologists began to adopt newer and stronger fixatives in histological work, and tried to adapt them for use in cell research as well. These fixatives were typically acidic chemicals applied to tissues to kill, preserve, and harden histological structures, in preparation for sectioning, staining, and mounting on microscope slides. As noted in the previous chapter, earlier cell theorists like Hugo von Mohl were already using nitric, sulphuric, and hydrochloric acids, as well as the traditional preservatives vinegar (acetic acid) and alcohol, to separate out and highlight particular cell structures. Von Mohl did so explicitly acknowledging that these acids killed, pickled, and (advantageously) modified tissues and cells for more careful examination under the microscope. But it was Flemming's revelations of chromosomal behavior that drew attention to the newest classes of fixative chemicals he used, many of which were acidic solutions of rare metals. The best known of these were osmic acid (osmium tetroxide), potassium dichromate, mercuric chloride (more commonly called "corrosive sublimate"), and picric acid (an explosive); Flemming either introduced or became a strong advocate for all of these in cytology and histology around 1878–84.[6]

Traditionally the small historiography of late nineteenth-century microscopy (as opposed to early nineteenth-century microscopy) has focused on the continued improvement in microscope optics, the development of the microtome for thin sectioning of organs and tissues, and the role of the aniline dye industry in producing new biological stains.[7] Fixation is not a well-covered topic:

6. Brian Bracegirdle, *A History of Microtechnique: The Evolution of the Microtome and the Development of Tissue Preparation* (London: Heinemann, 1978), 60–64; Jutta Schickore, *The Microscope and the Eye*, chapter 8.

7. On the history of late nineteenth-century microscope optics, see: Stuart M. Feffer, "Ernst Abbe, Carl Zeiss, and the Transformation of Microscopical Optics," in *Scientific Credibility and Technical Standards in 19th and Early 20th Century Germany and Britain*, ed. Jed Z. Buchwald (Dordrecht: Kluwer, 1996), 23–66; Savile Bradbury, *The Evolution of the Microscope* (Oxford: Pergamon, 1967), chapters 6–7; and Hubert de Martin and Waltraud de Martin, *Vier Jahrhunderte Mikroskop* (Wiener Neustadt: Weilburg-Verlag, 1983). Two older histories of staining technique in cytology are S.I. Kornhauser, "The History of Staining the Development of Cytological Staining," *Biotechnic & Histochemistry* 5, no. 4 (January 1930): 117–25; and H. J. Conn, *The History of Staining* (Geneva, NY: Biological Stain Commission, 1933).

The dominance of the historiography related to aniline dye staining has much to do with its relationship to the origins of the pharmaceutical industry: Paul Ehrlich (1854–1915) became very skilled at histological staining in the 1870s through his doctoral research, and later developed his theories of staining specificity into a program of chemical-

Brian Bracegirdle's classic history of the development and use of the microtome 1860s and '70s contains in a few pages the only history of fixation as such, while Jutta Schickore discusses anatomists' debates in the 1830s about the proper handling of nervous tissue in between dissection and observation.[8] Yet the episodes, scientists, and their experiments covered in this chapter are not only frequently cited by historians of science: they also were frequently cited by the very biologists who were arguing about fixatives and protoplasmic structure. Neil Morgan and Robert Olby discuss the fixation controversy but briefly (and then only in reference to William Bate Hardy) as an episode in the larger debates about cellular structure versus function; otherwise, historians have tended only to briefly make note of these episodes as markers of whose genetic or cellular theories were being elevated or dismissed.[9] But biologists working in the 1890s knew that the stakes of their research were high, that their methods were marginal, and their terminology was idiosyncratic: the constant references and retellings of their own history were an important way to advance a broad claim about the structure of protoplasm without dedicating an unreasonable amount of time surveying every possible kind of plant and animal protoplasm. This led to an acute vocabulary problem, one reviewer

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pharmaceutical therapy. On Ehrlich, aniline dye stains, and pharmaceuticals, see: Timothy Lenoir, "A Magic Bullet: Research for Profit and the Growth of Knowledge in Germany around 1900," *Minerva* 26, no. 1 (1988): 66–88; J Liebenau, "Paul Ehrlich as a Commercial Scientist and Research Administrator," *Medical History* 34, no. 1 (January 1990): 65–78. On Ehrlich's use and promotion of new biological stains for metabolism research in the 1870s and '80s, see Anthony S. Travis, "Science as Receptor of Technology: Paul Ehrlich and the Synthetic Dyestuffs Industry," *Science in Context* 3, no. 2 (1989): 383–408; and, "Models for Biological Research: The Theory and Practice of Paul Ehrlich," *History and Philosophy of the Life Sciences* 30, no. 1 (2008): 79–97.

8. Brian Bracegirdle, *A History of Microtechnique*, 60–64; Jutta Schickore, *The Microscope and the Eye*, chapter 8. On debates about the uses of thin sectioning, see also Lynn K. Nyhart, *Biology Takes Form*, 201–4.

9. Robert C. Olby, "Structural and Dynamical Explanations in the World of Neglected Dimensions," in *A History of Embryology*, ed. T. J. Horder, J. A. Witkowski, and C. C. Wylie (Cambridge: Cambridge University Press, 1986), 275–308; Neil Morgan, "The Strategy of Biological Research Programmes: Reassessing the 'Dark Age' of Biochemistry, 1910–1930," *Annals of Science* 47, no. 2 (March, 1990): 139–50; and "Reassessing the Biochemistry of the 1920s: From Colloids to Macromolecules," *Trends in Biochemical Sciences* 11, no. 4 (April 1, 1986): 187–89. For examples of brief mentions of the controversy over fixation artifacts, see: Jan Sapp, *Genesis: The Evolution of Biology* (Oxford: Oxford University Press, 2003), ch. 8; William Bechtel, *Discovering Cell Mechanisms: The Creation of Modern Cell Biology* (Cambridge: Cambridge University Press, 2008), 81; Robert Olby, *The Path to the Double Helix* (Seattle: University of Washington Press, 1974), 97–98; Thomas Steele Hall, *Ideas of Life and Matter: Studies in the History of General Physiology, 600 BC–1900 AD* (Chicago: University of Chicago Press, 1969), 338–40; Gilbert Ling, *In Search of the Physical Basis of Life* (New York: Plenum Press, 1984), 38.

complaining that, "The early specialization of a large number of the younger workers in this line has led to the publication of many articles on the subject utterly devoid of literary form, filled with local and personal terms, uselessly recounting technique, and giving the most merciless repetition of details of observation with no attempt to summarize the results, or give the general significance of the phenomena described."[10] So rather than accounting for all of the subtle changes in protoplasmic theory and vocabulary, this chapter tries to answer a different set of questions to find a more synthetic and contextualized way of understanding the state of protoplasm theory at the end of the nineteenth century. What did biologists think fixatives could do? How did biologists think fixatives worked? How did they study and respond to the unintended effects of such an important technique?

Arguments in the 1880s and 1890s about the effects and errors caused by fixation were not simply contained within a discourse about method, what Schickore calls a "second-order" scientific discourse: they fundamentally changed how biologists thought about the physical state of matter and the physical basis of life. This chapter will argue and demonstrate that ideas of protoplasmic structure shifted from visual/anatomical theories to theories of physical-chemical state. As a direct result of Flemming's 1882 observation of fixation artifacts by osmic acid, arguments that the protoplasm was "granular" or "reticular" gave way to claims that the protoplasm was a heterogeneous emulsion or a fluid capable of coagulation. What began as an esoteric debate about cytological technique had by 1899 transformed what being materialist in biology meant, creating an intellectual environment in which cell and protoplasm research could be done with hardly any examination of cells or protoplasm.

In other words, what began as a debate over what protoplasm looked like under the microscope was resolved by transforming the kind of matter protoplasm essentially *was*. So by 1899,

10. D. T. MacDougal, review of *The Fixation, Staining, and Structure of Protoplasm*, by Alfred Fischer, *Science* 10, no. 248 (September 29, 1899): 451–53, on 452.

not only could William Bate Hardy (1864–1933) theorize about protoplasm by studying blocks of fixed gelatin, but he could theorize about the structure and nature of colloidal gelatin by studying the infinitely more complex protoplasm. In this small but important corner of biological research, both the methodological and metaphysical distinctions between living matter and non-living matter collapsed. As Morgan has argued, "Having demolished one bridge between chemistry and morphology, Hardy turned to colloid science to build another."[11] This chapter broadens Morgan's argument. Rather than systematically tell a history of the development fixation techniques, this chapter will examine how controversies about fixation methods led biologists to embrace colloid chemistry at the turn of the century, as they tested and argued about fixatives using artificial colloidal preparations. What had been merely a laboratory control became a model of living matter, and a habit that began as a breezy way of dismissing older theories of protoplasmic structure as a result of poor technique eventually established both a methodological and an ontological equivalence between complex living matter — protoplasm — and simple, non-living colloidal materials.

a. Osmic acid, protoplasmic frameworks, and Flemming's fibrillar theory

The consensus coming out of the 1870s was that protoplasm had an interconnected "reticular," "network," "mesh," or "framework" structure, despite some minor differences among biologists over durability of the framework, the coarseness or fineness of the mesh and the size of the gaps in the network's open spaces.[12] In 1882, Flemming announced that he was abandoning this for

11. Neil Morgan, "The Strategy of Biological Research Programmes," 145.

12. At least this was Otto Bütschli's view in 1892, and Bütschli used the terms *"reticulären Bau," "Netzwerk," "Maschenwerk," "Gerüst,"* and sometimes combinations like *"Netzgerüst"* and *"Gerüstwerk"* without any distinctions between them. Since he was a partisan of a variation of the network theory, it is possible he was deliberately blurring these distinctions. At the same time, his is still the most thorough historical account of protoplasmic structure theories between 1861 and 1892. Otto Bütschli, *Untersuchungen über mikroskopische Schäume und das Protoplasma: Versuche und Beobachtungen zur Lösung der Frage nach den physikalischen Bedingungen der Lebenserscheinungen.* (Leipzig: Wilhelm Engelmann, 1892), 102–38; the English translation is Otto Bütschli, *Investigations on Microscopic Foams and on Protoplasm: Experiments & Observations Directed Towards a Solution of the Question of the Physical Conditions of the*

a *fibrillar* structure of overlapping, but not interconnected threads. He became one of the first biologists to suggest that reticular, interconnected structures might be the result of mishandling at any number of stages, including during fixation. He was especially concerned that a relatively new and very powerful fixative, osmic acid, was being applied carelessly by biologists who were eager to exploit this new tool.

Osmic acid was found to be a usable fixative by Max Schultze in 1864, but it was still a rather exotic addition to biological laboratories into the 1880s.[13] Long and concentrated exposure to osmium can completely blacken tissues, and the metal itself has an "extremely poisonous nature and offensive odor."[14] In the nineteenth century osmium was a byproduct of platinum mining from the Urals, and pure osmium had almost no commercial value; its use as a metal was limited to hardening fountain pen tips and making some early lightbulbs. Today osmium is recognized as the rarest naturally occurring element on the Earth, but its toxicity and limited application keeps its economic value relatively low. Biologists in the nineteenth century found two different ways of applying an osmium fixation: applying a diluted osmic acid solution directly to a sample, or by holding a sample over a container 1-2% osmic acid solution and allowing the caustic vapor to penetrate and darken the sample, over the course of a few minutes to twenty four hours, depending on sample's size.[15]

Flemming's colleague at Kiel, Carl Kupffer, had made a strong claim for the reticular structure of protoplasm in by fixing liver cells with osmic acid, at a sufficient strength to turn the

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Phenomena of Life, trans. E. A. Minchin (London: Adam & Charles Black, 1894), 157–218.

13. Max Schultze and M. Rudneff, "Weitere Mittheilungen über die Einwirkung der Ueberosmiumsäure auf thierische Gewebe," *Archiv für mikroskopische Anatomie* 1 (1864): 299–304; Paul Mayer, "Über die in der Zoologischen Station zu Neapel gebräuchlichen Methoden zur mikroskopischen Untersuchung," *Mittheilungen aus der zoologischen Station zu Neapel* 2, no. 1 (1879): 1–27.

14. Julius Ohly, *Analysis, Detection and Commercial Value of the Rare Metals: A Treatise on the Occurrence and Distribution of the Rare Metals and Earths, the Methods of Determination and Their Commercial Value in the Arts and Industries with a Historical and Statistical Review of Each* (Mining Reporter Publishing Company, 1907), 89-92.

15. For a contemporary account of the use of osmic acid, see Thomas B. Redding, "Osmic Acid: Its Uses and Advantages in Microscopical Investigations," *Proceedings of the American Society of Microscopists* 4 (1882): 183–86.

cells pale greyish-brown.[16] As a test case Flemming chose the filamentous algae *Spirogyra*, which he noted was, usually assumed to be far more light and fluid in texture than liver cells. He described how,

> If I place a *Spirogyra* filament in 1-2% osmic acid and after a good browning examine it, I find in place of a light cell sap of the living observed cell, which passes between the delicate protoplasmic strands, it is all very dense, gray-colored, fine-grained networks or frameworks, as in Fig. A, which shows a piece of such a strand in high magnification.[17] (Figure 2.1)

Flemming describes laying or placing, (*"lege"*) the *Spirogyra* filament *in* 1-2% osmic acid, rather than suspending (*"aussetzen"*) a sample over osmic acid vapor, as Kupffer had. This was a distinction with a difference. Kupffer had also suggested that the osmium vapor treatment stop when the sample became just lightly browned (*"bis zur leichten Bräunung"*), for only a few minutes, whereas Flemming gleefully describes a "good browning" (*"nach guter Bräunung"*) of the same. It is unclear whether Flemming was deliberately changing Kupffer's preparations, if he was simply using different language to describe the same, or if he was exaggerating for rhetorical effect, but his argument remained. For Flemming, overuse and overexposure to osmic acid could create a net-like artifact in protoplasm, a structure that protoplasm did not naturally have.

Flemming believed that osmium produced the net by acting too powerfully and too quickly on the delicate cell. "When applying mere chromic acid and picric acid," Flemming noted, "a much greater meandering, kinking, and shrinking of the chromatic fibers happens, as it appears to correspond with their state in nature. I explain this through the fact that these acids kill more slowly and leave room for some changes during the cell's death."[18] On the other hand, with osmic acid alone "the evils are much greater," and he complained that workers in the 1870s were using very

16. Carl Kupffer, "Ueber Differenzirung des Protoplasma an den Zellen thierischer Gewebe," *Schriften des naturwissenschaftlichen Vereins für Schleswig-Holstein* 1, no. 3 (1875): 229–42, on 231.

17. Walther Flemming, *Zellsubstanz, Kern und Zelltheilung*, 50.

18. *ibid.*, 381.

strong osmium solutions or exposing tissues to osmium vapors for too much time.[19] Flemming preferred a very dilute a mixture of fixative chemicals as a way to take advantage of the different powers of the different fixatives to highlight different structures, while not brutalizing the contents of the cell. He initially tried a mixture of 0.1% osmic acid and 0.25% chromic acid, but found that while the specimens were well conserved, staining to increase contrast was almost impossible. "Flemmings Gemisch," or Flemming's solution, would eventually be solution of 0.1% osmic acid, 0.25% chromic acid, and another 0.1% of acetic acid: osmic acid and chromic acid successfully revealed fibrous structures like chromosomes and nuclear spindles, while acetic acid made them readily take up stains. He also recommended a relatively short 30 minute exposure, then a thorough washing out with water.

It was possible, however, to read Flemming's 1882 book and miss his sporadic cautionary notes about fixation artifacts: his genuine blockbuster was the discovery of mitosis, in which his use of several different fixation regimes played an essential role. Flemming was by then already a famous reformer and innovator in both staining and fixation procedures, known for promoting new methods: his name is still attached to a fixative, Flemming's solution, and to a complex staining regime, Flemming's triple stain.[20] In addition, Flemming's warnings about fixations in 1882 relied on any reader's trust in his judgement that certain preparations produced specimens that were "not as true to nature" or otherwise, and he gave little explanation for why specific real or false structures might appear. His writing typically focused on which fixative was good for revealing a given structure, rather than warn his colleagues off of other fixation regimes. Through the 1880s more

19. *ibid.,* 380.

20. Harold A. Davenport, *Histological and Histochemical Technics* (Philadelphia: W. B. Saunders Co., 1960). Kornhauser and Conn both called Flemming "the father of modern technic" in staining and fixation; S. I. Kornhauser, "The History of Staining the Development of Cytological Staining," 118.

generally, fixation regimes would rely on more concentrated and powerful chemicals, culminating in Richard Altmann's study of protoplasmic structure in 1890 (discussed below).

As subsequent biologists turned their attention to *why* fixatives worked the way they did, Flemming's 1882 book, and specifically the two pages discussing artifacts in *Spirogyra* caused by 1–2% osmium solution, would be a touchstone, referenced repeatedly for the next two decades.

b. Artifice and the coagulating protoplasm

It is not clear exactly why the Göttingen plant physiologist Gottfried Berthold (1854-1937) was inspired to compare Flemming's osmium-saturated *Spirogyra* filament with chicken egg white specifically, but he would later be recognized as the first to use an non-living substance to show that the protoplasmic "net" was an artifact of fixation. Berthold's comment was brief, and is reproduced here in its entirety:

> It is not difficult to understand how reagents, which kill the plasma body, have the capacity to produce scaffold-like precipitates in coagulable substances. That such framework-shaped coagulates can be obtained from the cell sap has been described by *Flemming* (loc. cit. pp. 50, 51) for *Spirogyra*. Before the appearance of Flemming's book I myself had called attention to a similar occurrence, observed in threads of *Zygnema cruciatum* treated with soda solution and stained with aceto-carmine. Here, too, I obtained the most beautiful reticular precipitate in the cell sap. The same produced in the cell sap of *Urtica* hairs with the addition of alcohol, and especially nice ones can be obtained when one shakes a drop of chicken egg white with distilled water. It then deposits flakes that show a beautiful "framework-like structure." By treating the same egg white with diluted iodine solution, the result is that fine dotting which so often recurs in [Frank] *Schmitz*'s descriptions [of the reticular structure].[21]

This matter-of-fact statement potentially marked a significant epistemological and methodological shift from all of the protoplasm theorists who had come before, including Walther Flemming. Flemming, after all, had waded into the debate about protoplasmic structure by showing that a particular structure could arise through poor preparation procedure, and rhetorically he demonstrated this by improperly fixing a *Spirogyra* cell. Berthold was a full supporter of Flemming's

21. Gottfried Berthold, *Studien über Protoplasmamechanik* (Leipzig: Arthur Felix, 1886), 61-62.

fibrilar theory of protoplasmic structure. Berthold amplified Flemming's critique, not by systematically examining cells and reagents, but rather by breezily comparing a stinging nettle cell to a frothed drop of chicken egg white stained with iodine.

Berthold's egg white demonstration might have been a mere footnote if the rather obscure Breslau (now Wrocław) botanist and forester Frank Schwarz (1857-1928) had not expanded on the idea in his larger study of the physiological chemistry of plant protoplasm. Taking Berthold's cue, Schwarz began with chicken egg white fixed with either alcohol, 1% picric acid, Flemming's solution, or iron chloride.[22] Schwarz's comparison did not end there: he also prepared and applied fixatives peptone solution, joiner's glue, gum arabic, gelatin, several different tree resins (spruce, cypress, mastic, and Malabar kino), an exotic preparation of copper ferrocyanide, and an infamous boiled glue solution known as Moritz Traube's "*β-Leim.*"[23] He even took care to adjust the preparations to have "a similar consistency as the cytoplasm," though he did not specify how he made or proportioned these preparations. Berthold, on the other hand, had not even introduced his chicken egg white with its own sentence.

Yet Berthold and Schwarz shared the same rationale for the comparison: protoplasm and these non-living substances were both mixed, "coagulable" substances that were capable of separating out (*Entmischung*) into component parts. Berthold argued that, rather than having any obvious

22. Frank Schwarz, "Die morphologische und chemische Zusammensetzung des Protoplasmas," *Cohns Beiträge zur Biologie der Pflanzen* 5 (1887): 1–240, on 143. It is not clear if Schwarz was using ferric chloride or ferrous chloride.

23. *ibid.,* 143–47. Traube's *β*-Leim was glue that had been boiled for at least 12 hours, and precipitated by dropping it into a 0.5–6% tannic acid solution; the precipitation membranes that resulted were infamous for Traube's claims to have created living, artificial cells, and for being the material basis for Wilhelm Pfffer's osmosis studies. On Traube, see J. Reynolds Green, *A History of Botany, 1860-1900: Being a Continuation of Sachs "History of Botany, 1530-1860"* (Oxford: Clarendon Press, 1909), 250–52; Henrik Franke, *Moritz Traube (1826-1894): vom Weinkaufmann zum Akademiemitglied: der aussergewöhnliche Weg des jüdischen Privatgelehrten und Pioniers der physiologischen Chemie*, Studien und Quellen zur Geschichte der Chemie, Bd. 9 (Berlin: Verlag für Wissenschafts- und Regionalgeschichte, 1998). Moritz Traube, "Experimente zur physikalischen Erklärung der Bildung der Zellhaut, ihres Wachsthums durch Intussusception und des Aufwärtswachsens der Pflanzen," *Botanische Zeitung* 33, no. 4–5 (January 1875): 56–70; Moritz Traube, "Experimente zur Theorie der Zellenbildung und Endosmose," *Archiv für Anatomie, Physiologie, und wissenschaftliche Medezin*, 1867, 87–165.

visible internal structure, the protoplasm was "an emulsion with a more or less fluid consistency," and "a highly complicated mixture" ("*eine hoch complicirte Gemische*") of many different substances into one.[24] The diverse morphology of different kinds of protoplasm would then come from the protoplasm's powers to differentiate (*Differenzierungsvorgänge*) its component parts; this was by analogy, Berthold wrote, to the way essential oil dissolved in alcohol precipitates into droplets when water is introduced.[25] Such a process, Berthold suggested, would explain how non-protoplasmic substances like resins, oils, and sugars could concentrate naturally within or around the protoplasm of certain kinds of plant cells.[26] And even if Berthold did not think the protoplasm had an underlying network or framework structure, he suggested that "we will have to leave completely open the possibility that differentiation products or precipitates may occur in the form of a fine scaffolding in the plasma body's normal course of life."[27] In other words, Berthold thought the protoplasm's ability to precipitate its own products was itself similar to the way chicken egg white could precipitate into the "framework-like structure" he had described: what was common was the process of precipitation and separation.

Surprisingly, perhaps, the mere idea that both protoplasm and gelatin were coagulable or capable of precipitating did not lead Schwarz to try different, non-cytological methods of coagulating either protoplasm or his artificial preparations; nor did he try some of the more obvious physical methods like cooking, or applying electrical or mechanical shock. Instead, Schwarz stuck exclusively to histological fixatives, in order to establish their visual similarities (Figure 2.2). For all of Schwarz's sophisticated study of different non-living materials, he came to much the same conclusion

24. Gottfried Berthold, *Studien über Protoplasmamechanik*, 64.

25. *ibid.,* 64–65.

26. *ibid.*, 66–67.

27. *ibid.*, 62.

that Berthold had before him: "In my view the cytoplasm has no preformed net or framework, but a part of it may be able to reorganize into fibers and strings. Consequently," Schwarz continued, "I must accept that the cytoplasm is a mixture ("*eine Mischung*"), in which under certain circumstances the solid, tough substances can separate from the dissolved, fluid ones."[28]

Not only were Berthold and Schwarz comparing protoplasm to egg white or gelatin, they were making the comparison by applying the same set of methods, originally developed for research on cells and tissues. The very idea that protoplasm was a mixture or emulsion capable of separating out had been inspired by Flemming's deliberately faulty fixation of the *Spirogyra*. Out of Flemming's passing observation, a rather remarkable new rhetoric developed about the structure and behavior of both protoplasm and non-living substances. As the methodological similarities for studying them were being established, the ontological divisions between living protoplasm and non-living glue were beginning to break down — all this, it should be noted, in the absence of any overheated rhetoric about vitalism or materialism.

The idea that protoplasm was an emulsion received far wider attention in 1892, when the protistologist Otto Bütschli's (1848–1920) "alveolar" ("*wabig*" or "*alveolärer*") theory became one of the most widely accepted theories of protoplasmic structure for some time. Bütschli argued, first, that protoplasm was an emulsion, and that second, that all emulsions could create an "alveolar" structure when examined under the microscope. He acknowledged that he was resurrecting a version of the old network theory of the 1870s. Yet rather than make his case exclusively on the basis of extensive observation of living cells, Bütschli began with extensive observations of olive oil foams, and then devoted a similar amount of page space to observations of protozoan, plant, and animal cells that matched his descriptions of olive oil emulsions (Figure 2.3). To prepare the foam, Bütschli

28. Frank Schwarz, "Die morphologische und chemische Zusammensetzung des Protoplasmas," 136. The whole passage is emphasized in the original.

created a paste from "olive oil that has stood for a long time in a bottle in the laboratory," added pulverized salt, sugar, or other soluble substance, and then added "ordinary Heidelberg tap-water."[29] Bütschli examined the olive oil foam, soaps, and inks and dyes under the microscope, estimating the volume of the alveoli, heating and cooling the foams, applying electric current, and watching the foams slide around and off the microscope slide (Figure 2.4). Bütschli's became so proficient at making protoplasm-like foams out of olive oil that he was even able to play a practical joke on his colleagues: "I have often placed preparations of the foam before some of my colleagues, who were themselves not inexperienced in the investigation of protoplasmic structures, and were quite unbiassed in their opinions, and asked them what they believed the object to be which they were shown, and the nature of which they were quite ignorant. One of them guessed it to be an egg cell, another thought it was Rhizopod protoplasm, or something of the sort."[30] Living protoplasm and stale olive oil were, by the 1890s, becoming indistinguishable from each other, even to experienced laboratory biologists.

c. *Alfred Fischer's catalog of fixation artifacts*

Paying little heed to the concerns raised by Flemming, Berthold, and Schwarz, in 1890 the Leipziger anatomist Richard Altmann (1852–1900) developed a "granular" theory of protoplasmic structure, through an enthusiastic use of powerful fixative chemicals (Figure 2.5). His eponymous formula was a mixture of 2% osmic acid and 5% potassium dichromate; at other times he also used plain osmic acid, osmium dichromate, corrosive sublimate (mercuric chloride), all standard fixatives in the 1880s. Yet Altmann also had a penchant for far more exotic fixatives, including: mercuric

29. Otto Bütschli, *Investigations on Microscopic Foams and on Protoplasm*, 8.

30. *ibid.,* 85.

oxide or chrome trioxide dissolved in nitric and formic acids, potassium tetraiodomercurate(II) mixed with tannic acid, mercuric bromide, and a mix of chromic acid with ammonium heptamolybdate.[31] Using this increasingly exotic range of fixation preparations, as well as his own staining regimes, Altmann argued that the fundamental units of the protoplasm were "bioblasts," tiny, bacteria-like granules, each an individual, elementary unit of life.[32]

Most of the skepticism towards Altmann revolved around the privileged status he gave to his granular "elementary organisms," but one of Altmann's colleagues at Leipzig, the cryptogamic botanist Alfred Fischer (1858–1913) was far more suspicious of the methods Altmann used to reveal their existence.[33] Fischer's initial critique of Altmann's granular bioblast theory began in 1894, and it was both brief and devastating.[34] Fischer applied five different fixative chemicals to a 2–10% commercial peptone (protein) solution, including Altmann's own mixture of 1% osmic acid with 2.5% potassium dichromate.[35] Each fixative produced a precipitate that looked exactly like Altmann's protoplasmic granules. These granular precipitates could even be washed, dried, and stained like bacteria, using aniline dyes, hematoxylin, picrocarmine, etc. To Fischer this was proof that Altmann's preparation techniques were producing microscopic objects that looked like bacteria or protoplasmic

31. Richard Altmann, *Die Elementarorganismen und ihre Beziehungen zu den Zellen* (Leipzig: Veit, 1890), 27–32; Alfred Fischer, *Fixirung, Färbung und Bau des Protoplasmas: Kritische Untersuchungen über Technik und Theorie in der neueren Zellforschung* (Jena: Fischer, 1899), 28–29, 33–34. It is difficult to translate the last three; Fischer refers to them as "Jodkaliumquecksilberjodid," "Bromkaliumquecksilberbibromid," and "Chromsäure und molybdänsaures Ammoniak."

32. On Altmann's bioblasts, see Andrew Reynolds, "The Theory of the Cell State and the Question of Cell Autonomy in Nineteenth and Early Twentieth-Century Biology," *Science in Context* 20, no. 1 (2007): 71–95, on 79.

33. For a small sample of the skepticism towards Altmann's granular theory, see Otto Bütschli, *Untersuchungen über mikroskopische Schäume und das Protoplasma,* 126–29; Edmund B. Wilson, *The Cell in Development and Inheritance*, 1st ed. (New York: MacMillan, 1896), 21–22

34. Alfred Fischer, "Zur Kritik der Fixirungsmethoden und der Granula," *Anatomischer Anzeiger* 9 (1894): 678–80.

35. Fischer wrote that he obtained all of his various protein solutions locally, from the Leizpiger chemist Georg Grübler, whose company was known for selling and marketing new aniline dyes for biological laboratory work. For more on Grübler see M. Titford, "George Grubler and Karl Hollborn: Two Founders of the Biological Stain Industry," *Journal of Histotechnology* 16, no. 2 (June 1993): 155–58; and, "Comparison of Historic Grübler Dyes with Modern Counterparts Using Thin Layer Chromatography," *Biotechnic & Histochemistry* 82, no. 4/5 (August 2007): 227–34.

granules, even when applied to sterile, non-living, laboratory preparations of protein solution. Altmann's granules, in other words, were not natural structures, but merely fixation artifacts.

The peptone solution Fischer used was initially just contained in a test tube, but he soon went quite a bit further: Fischer began inject peptone solution into elder pith (*Hollundermark*) to create artificial "cells," measuring about 2x5mm, which he then "fixed." At first Fischer was merely interested in showing that fixation artifacts could be produced in a more natural, tissue-like physical setting, where the fixative needed time to penetrate, first through the whole mass of the (artificial) tissue, then through each cell wall. Fischer fully expected to find Altmann-esque granules distributed more unevenly through the elder pith than in a the test tube, but he was unprepared for exactly how unevenly they would be distributed:

> In the middle of the cell was a nucleus-like body, from which radiated on all sides beautiful, thin threads (*Strahlungen*) of small and large granules (*Körnern*) that were anastomosed with one another, running out to the wall. The very image of a plant cell emerged, in the middle of which was a cell nucleus suspended on protoplasmic threads…If a 10% peptone solution is injected, one obtains threads made of giant microsomes, while with a weaker solution they are composed of finer grains. By the suitable addition of some hemoglobin or gelatin one can notably increase the beauty of the nucleus. Naturally, these artificial cell structures can be stained.[36]

Fischer's experiment with artificially filled elder pith cells considerably amplified his concerns about fixative chemicals. Berthold and Schwarz had pointed to problems with specific fixative regimes, while also arguing that fixatives show that protoplasm is coagulable. Now in 1894, Fischer took the next step, arguing that all fixatives coagulate the protoplasm, and that there was something much more profoundly problematic about the way biologists had been using and arguing with fixative preparations since Flemming. Implicitly referring to Altmann, Fischer complained that there was a "prevailing tendency to sense (*wittern*) a special organ of the cell in every strongly stained granule and globule, and to attribute each one of these to the powers of individual fixation methods." In order to avoid "these errors, in which modern cell research only too gladly loses itself," Fischer

36. Alfred Fischer, "Zur Kritik der Fixirungsmethoden und der Granula," 680.

maintained that "it would be advisable for the study of the finer structures of the protoplasm and nucleus to return to a closer attention to living cells."[37] His alarmist attitude rankled even some of his friends, who wrote in his obituary that his concerns about fixation "were perhaps too broad."[38] Fortunately, Fischer soon found a simple, reassuring explanation for the alarming nucleus-like structure: it had been a real nucleus, not a fixation artifact, a remnant of the formerly living cell in the elder.[39]

Although he was wrong about the nucleus artifact, Fischer's continued experimentation with the false "nucleus" and "threads," and his efforts to make them more "beautiful" through adding hemoglobin and gelatin, led him to a crucial discovery. Fischer found that a mixture of different protein solutions would precipitate and separate out in different ways when a fixative solution was added. A mixture of peptone and serum albumin, for example, produced "beautiful peptone granules embedded in the fine, protoplasmatic clots (*Gerinnsel*) of the serum albumen" when fixed.[40] Emboldened, Fischer tried a more complicated solution of five different protein preparations, and found that different fixatives precipitated out different combinations of granules and coagulates:

> Since the mixture was kept almost neutral, slightly alkaline, Altmann's mixture gave only a uniform coagulate, in contrast to the beautiful peptone granules of different sizes created by sublimate, chromic acid, and Flemming's solution, depending on the fixative, embedded in a five-component coagulate of serum albumin, ovalbumin, paraglobulin, casein, and hemoglobin. In addition, osmic acid precipitated out large granules within a coagulate that appears to have only three parts, serum albumin, paraglobulin, and hemoglobin.[41]

Fischer had stumbled upon the fact that fixative chemicals had the power to differentiate mixtures that had previously appeared homogenous. This gave Fischer a hint for how to create a general

37. Alfred Fischer, "Neue Beiträge zur Kritik der Fixirungsmethoden," *Anatomischer Anzeiger* 10 (1895): 769–77, on 775.

38. Johannes Behrens, "Alfred Fischer," *Berichte der deutschen botanischen Gesellschaft* 31 supp. (October 1913): 111–17, on 115.

39. Alfred Fischer, *Fixirung, Färbung und Bau des Protoplasmas*, 206–209.

40. Alfred Fischer, "Neue Beiträge zur Kritik der Fixirungsmethoden," 772.

41. *ibid.*, 774.

theory of fixation, and how to deal with fixation artifacts: "If the components and the reactions of a mixture are known, then one will always be able to predict the effects of various fixatives, without fail." However, his confidence in the power of fixatives had its obverse side: "If one grants the fixative the ability to reveal and clarify the existing structures of the cell, then it is a logical fallacy to speak of a good and bad fixation," Fischer wrote in 1895, arguing that all fixatives precipitated or coagulated *something*. "Where a fixative does not yield to a schematic image, the problem is not in the fixative, but rather in the fixed object itself: that is, in its living structure."[42] This was Fischer's essential insight: that even if a structure shown after fixation was an artifice, the process by which that artifice had been produced was natural, and thus revealed something about the protoplasm's original state.

Fischer's 1899 monograph on *The Fixation, Staining, and Structure of the Protoplasm* built on this insight, attempting to standardize both fixation technique and to catalog all possible effects fixative chemicals might have. On the one hand, Fischer succeeded in creating a guide for best practices of fixation, but he failed on the other hand at comprehensively cataloguing every possible fixation effect. Reprising Flemming's figure and footnote from 1882, Fischer noted the problematic nature of osmic acid, but he emphasized alternative preparations. "Flemming (I, p. 51, Fig. A) described very strong osmium precipitations in the cell sap of *Spirogyra*, which other reagents," Fischer added, "such as diluted acetic acid, iodine solution, potassium dichromate, chromic acid, and picric acid do not cause."[43] Along these lines *Fixation, Staining, and Structure* reads as a systematic catalog of the precipitations of a six commercial protein solutions and three nucleoprotein

42. Alfred Fischer, "Neue Beiträge zur Kritik der Fixirungsmethoden," 775.

43. Alfred Fischer, *Fixirung, Färbung und Bau des Protoplasmas*, 14.

solutions,[44] each one treated with up to nineteen different fixative preparations.[45] The proteins were broadly categorized into two groups depending on what kind of precipitates each solution produced, granules (*Granulabildner*) and clots (*Gerinnselnbildner*). Then, each protein was described after treatment. For example, with peptone, Fischer provided the following:

> a) *No precipiation*: nitric acid, acetic acid, chromic acid, potassium dichromate, formaldehyde (10%), Flemming's solution.
>
> b) *Slightly soluble precipitation in water*: alcohol, picric acid.
>
> c) *Insoluble precipitation in water*: sublimate, platinum chloride, osmic acid, Altmann's mixture, Hermann's solution.[46]

Several of the descriptions of fixative effects were accompanied by figures showing the relative size of the precipitated granules or the fineness of the clotted structure (Figure 2.6); for a few of the granular precipitates, Fischer listed granules' average diameters, depending on the fixative used and the concentration of the protein solution. However, the most extravagant part of *Fixation, Staining, and Structure* was accompanied by its lone color plate: Fischer produced ten different mixtures of two or more of the protein solutions at his disposal, injected them into elder pith cells, then fixed and stained them according to common cytological practice (Figure 2.7). The result was a visual catalog, showing the effects of a variety of different common fixative preparations on a variety of different mixtures — mixtures, Fischer presumed, that might be present in some form in real cells.

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44. Fischer chose nine protein solutions available from the Grübler co. (see note 35, above) as being broadly representative of proteins as a whole; it is likely that, given the state of protein chemistry in the 1890s, this was the most thorough course of action Fischer could have taken. Fischer listed six whole proteins: serum albumin, ovalbumin, serum globulin, hemoglobin, casein, and conglutin. In addition he used proteins in three degrees of digestion: highly digested "deuteroalbumose," less-digested peptone, and the least digested "protalbumose" or "hemialbumose." Fischer also purchased yeast nuclein from Grübler, and extracted purer nucleic acid from the yeast nuclein himself. In addition, Fischer obtained nucleic acid from thymus from Albrecht Kossel, a physiologist from Marburg. *ibid.,* 4–6.

45. The nineteen fixatives were: nictric acid, acetic acid, osmic acid, potassium dichromate, *Altmann's Gemisch* (1% osmic acid + 2.5% potassium dichromate), potassium tetraiodomercurate(II), alcohol, acetone, picric acid, tannic acid, chromic acid, corrosive sublimate (mercuric chloride), platinum chloride, formaldehyde, osmic- acetic-acid, *Flemming's Gemisch* (0.25% chromic acid, 0.1% ea. osmic and acetic acids), *Hermann's Gemisch* (0.8% platinum chloride, 0.25% osmic acid, 5% acetic acid), Lysol (the disinfectant), and lye. Lysol and lye were notable for being the only strongly alkaline fixatives. *ibid.,* 7–29.

46. *ibid.,* 41.

As a manual or textbook for advanced students, Fischer's book was a comprehensive guide for the use of fixation regimes, one that was far more detailed and systematic than previous works that were devoted to specific cell-anatomical structures. As a best-case-scenario, Fischer demonstrated that certain fixatives would not permanently create artifacts in certain proteins: with careful practice, Fischer's book was an aid for avoiding or ameliorating some fixation artifacts. Read this way, Fischer was making a very conservative statement within cytology: used properly, fixatives were excellent tools to reveal specific structures. Fischer even pushed this consensus slightly forward. His detailed cataloging of proteins and fixation-precipitation reactions made it possible to conduct a more detailed microchemical analysis of the dissolved proteins and nucleic acids in protoplasm, and even locate specific kinds of proteins in specific parts of the cell. If in its natural state the protoplasm looked like a clear, homogenous slime, Fischer argued that fixative chemicals might at the very least separate out nucleic acids from the proteins, and the granule-precipitating proteins from the ones that formed clots.[47] This analysis was crude compared to the kind of histochemical *staining* that Paul Ehrlich was promoting at the time for measuring oxidative activity (and with which Fischer was quite familiar), but staining alone could not identify proteins, even within Fischer's limited protein taxonomy.[48]

Fischer's fundamental problem was not in his ability to predict the effects of fixatives on all of these protein solution mixtures: his fundamental problem was that there were too many of these effects, and more variables than he had anticipated. Especially when he used the elder pith, the time and temperature of the fixation process, as well as the concentration of the fixing fluid, became additional physical variables. Between the physical variables and the nineteen fixatives at his disposal, Fischer found that the differences among precipitation effects were could be too small to measure; in

47. *ibid.,* 57–58.

48. See note 44, above.

one case Fischer noted that solutions of nuclein, nucleic acid, hemoglobin, globulin, albumin, and casein were all capable of producing identical structures.[49] Worse, hemoglobin could produce either granular or coagulated precipitations, depending on the fixative used, foiling even Fischer's basic categorization for precipitation types. Consequently, his hope to be able to identify substances in cells by comparing protoplasmic fixation artifacts with his artificial preparations seemed fraught, at best. In his ten experiments with mixtures of protein solutions, the resulting structures were so similar that he could hardly tell them apart. It sometimes seemed that many different substances once fixed could appear the same, *and* that the same substance fixed could appear in many different ways.

Fischer ultimately argued that protein structures were *polymorphic*, both in their natural and fixed state — and so too, therefore, was protoplasm. Fischer recalled that since 1861, Ernst Brücke had pushed biologists to find a grand unifying theory of the "essential architectonic element" of the protoplasm, in the same way Schleiden and Schwann had done with plant and animal tissues.[50] Now, in 1899, Fischer wanted to turn Brücke's injunction on its head: the cell might be a universal theory of living structure, but cells were certainly not all identical. The substances the cell and protoplasm were made of, Fischer noted, were capable of dramatic transformations both in their living and in their fixed state:

> The basic physical properties of the protoplasm, which is a fluid, are in general neither nullified nor intensified by certain developmental stages of seemingly solid precipitations, such that the desire of numerous cell morphologists for a solidly constructed structure of the bearer of life can be fulfilled through the differently shaped precipitates, sometimes persistent and sometimes quickly disappearing, whose physical states fluctuate from viscous to solid.[51]

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49. *ibid.,* 281–82.

50. *ibid.,* 294.

51. *ibid.,* 272; the original text is printed entirely in italics. ("Durch solche verschieden gestaltete, bald länger bestehende, bald schneller wieder verschwindene Ausfällungen, deren Aggregatszustand vom zähflüssigen bis zum festen schwanken wird, wird im Allgemeinen die physikalische Grundeigenschaft des Protoplasmas, die einer Flüssigkeit, nicht aufgehoben, nur würden auf gewissen Entwicklungszuständen die fester erscheinenden Ausfällungen so zunehmen und zu solchen Gebilden sich zusammenlagern können, dass der Wunsch zahlreicher Zellmorphologen nach einem fester

"Protoplasm" had always been a unified physiological concept in addition to a material one. With the redefinition of the cell *as protoplasm* in the 1860s, the search for a unified morphological and anatomical theory of the protoplasm became a crucial means by which biologists could hold together functional and structural theories of life. But here in this passage, Fischer wanted to warn biologists away from trying to find a single, universal structure of protoplasm: if protoplasm was acknowledged adjust itself to adapt to its environment (*e.g.,* dry, cold, digesting, in darkness, etc.), then some part of that adjustment must be to its composition. If its composition changed, Fischer reasoned, then the fixation artifacts, the "differently shaped precipitates," would be slightly different every time the biologist tried to fix the cell.

By dramatically expanding on the application of cytological techniques to non-living matter, Fischer believed he had accounted for the powerful controversies and disagreements about protoplasmic structure in the previous two decades. In fact this was perhaps the first time anyone had tried to articulate any theory of protoplasmic structure without looking at actual protoplasm: By 1899 Fischer viewed the wild swings from one structural theory to the next — the nets, fibrils, foams, and granules — as symptomatic of a deeper misunderstanding of both the material basis of life and of the chemical tools biologists wielded. Altmann's granular theory, in Fischer's view, was merely one of the worst excesses in the search for protoplasmic structure. For Fischer, the future of protoplasm research in the twentieth century still needed fixative chemicals, but they needed to be used with very different scientific aims and with much greater care.

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gefügten Bau des Lebensträgers erfüllt sein könnte.")

d. William Bate Hardy and the colloidal structure of protoplasm

For much of the 1890s William Bate Hardy was a young and talented member of Michael Foster's school of physiology at Cambridge, tasked with teaching the advanced histology course, and taking a research interest in the functional morphology of white blood cells in a range of vertebrate and invertebrate animals.[52] In 1899, however, his career took a dramatic turn, after he rather suddenly became concerned about histological fixatives. Citations in his earlier work show that he was engaged with German histology and anatomy journals, but there was no indication he had any special interest in fixation artifacts until 1899.[53] That year, Hardy published a landmark article in the *Journal of Physiology*, "On the Structure of Cell Protoplasm," again revisiting work on fixation artifacts by Flemming, Berthold, Schwarz, Bütschli, and Fischer in the last 17 years.[54] But whereas Fischer had tried to systematically catalog fixation artifacts, Hardy sought a general theory of the same by bringing to bear new concepts and techniques from colloid chemistry. Out of his investigation into fixation artifacts, Hardy not only redefined the protoplasm's structure as a colloid: he realigned a significant area of biological research towards the physical sciences, and he redefined himself as one of the most important colloid chemists of the early twentieth century.

On a superficial level, Hardy suggested that protoplasm was a colloid simply by definition: Dujardin had defined the protoplasm as "glutinous" long ago, and Thomas Graham (1805–1869) had defined colloids in the 1860s partly by their glue-like consistency and their inability to form pure, chemically analyzable crystals.[55] But Hardy was much more interested in using Graham's

52. Frederick Gowland Hopkins and FES, "William Bate Hardy, 1864-1933," *Obituary Notices of Fellows of the Royal Society*, 1934, 327–33. On the physiology course at Cambridge see Gerald Geison, *Michael Foster and the Cambridge School of Physiology: The Scientific Enterprise in Late Victorian Society* (Princeton: Princeton University Press, 1978), 303–4, and 304ff.

53. *Collected Scientific Papers of Sir William Bate Hardy*, ed. Eric K. Rideal (Cambridge: The University Press, 1936).

54. W. B. Hardy, "On the Structure of Cell Protoplasm," *The Journal of Physiology* 24, no. 2 (May 11, 1899): 158–210.

55. *ibid.,* 163.

colloid chemical vocabulary to redefine both coagulates and the process of coagulation — processes that through Berthold and Schwarz' research were now considered essential in understanding both protoplasm and fixation at the sub-cellular level. Graham's language of the sol-gel precipitation reaction was especially important to Hardy: in a colloid the sol is the more fluid or hydrated state, while the gel is the more solid state of a colloid, *e.g.,* when the sol is heated and some of the water evaporates. This analytical shift meant that, when Hardy proceeded to apply fixatives to egg white or gelatin, he focused on characterizing how the fluid colloid coagulated to appear to become more solid, examining the changing relations between the more fluid and solid parts of the whole colloid rather than just describing the appearance of the resulting coagulate, as Fischer or Schwarz had. For example, when Hardy fixed a block of gelatin with formaldehyde, he noted that the absence of visual changes was accompanied by a remarkable change in physical state: the water separated out from the solid parts of the gel.

> A hydrogel of gelatine holding ±13 grams solid in 100 c.c. will endure a pressure of ±400 lbs. to the square inch without separation of fluid. Fixation with formaline (formaldehyde) produces little superficial change. The jelly becomes firmer but retains its transparency. Its internal structure is however changed to such an extent that fluid can be expressed by hand-pressure alone.[56]

Thus, rather than attempting to defend a morphological theory of protoplasmic structure or fixative precipitations (*i.e.,* fibrillar, reticular, granular), here Hardy describes a physical change, the sudden inability of the gelatin to retain its water content. "To use *Graham's* terms," Hardy wrote, "the 'clot' shrinks and the 'serum' is expressed."[57] In addition, Graham and the other early colloid chemists supplied Hardy with a suite of scientific questions and experimental methods that would already have been familiar to colloidists. These included experiments with heat and cold, examining colloids when applying electric shock, applying acids and electrolytes, and applying both sudden mechanical shock and sustained compression or pressure.

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56. W. B. Hardy, "On the Structure of Cell Protoplasm," 174.
57. *ibid.,* 166.

In ponderous detail, Hardy measured and described the what he repeatedly referred to as "the mechanism of coagulation," in both living and non-living matter, using various vertebrate gland and white blood cells for the former. He even found that whether a net or a granular precipitation was produced depended on the concentration of the gel phase of the colloid; Fischer had only found such variability to depend on the kind of fixative chemical used. In other words, Hardy had found yet another reason for why so many different theories of protoplasm seemed to be both correct and utterly wrong: if one admitted that the concentration of proteins and electrolytes in any given cell was always changing, then the kind of structure visible in the protoplasm after fixation would change as well. Hardy also discovered that granular and fine-netted clots were not so fundamentally different: "The continuous net and the precipitate are not discontinuous states. They pass into one another with variations in concentration."[58]

By finding that both protoplasm and non-living colloids could produce the same range of fixation artifacts, Hardy was finally able to persuasively claim that protoplasm was a kind of colloid, and that, as was the case with gelatin or egg white, all fixative chemicals worked by dramatically rearranging any preexisting structure in protoplasm. Hardy's general theory of fixation was based on the pressure experiment: fixative chemicals irreversibly transformed and precipitated the gel phase of the colloid into an insoluble mass, separating it from the more fluid sol phase.

> The colloid substance of a cell does not become crystalloid as a result of the action of, *e.g.,* mercuric chloride. But though it does not become crystalloid, the action of the fixing reagent is such as to produce an insoluble modification of the colloidal matter…In the formation of an insoluble modification of a colloid from a soluble form, there is a separation of the solid from the liquid, so that the particles of the former adhere to form a framework which holds the liquid in its interstices.[59]

With this insight, Hardy was even able to suggest that only about 10% of the protoplasm consisted of more solid parts, using the same procedure he used with gelatin (noted above): by fixing orbital

58. *ibid.*, 172.

59. *ibid.,* 163.

gland, lymph, and marrow cells with osmium or corrosive sublimate and pressing out the fluid, he measured the proportion of fluid and solid, and compared them to fixed gelatin and egg white treated the same way.[60] Hardy also took thin sections of the resulting solid remnants and examined them under the microscope, showing them to be very similar (Figure 2.8). He concluded that cytological fixation was merely a particular case of the general phenomenon of the precipitation of colloidal aggregates out of a solution, making protoplasm a colloid. At least within the experimental systems of cytology, living and non-living colloids were essentially the same:

> Cell-protoplasm reacts to corrosive sublimate and osmic vapour in the same way as does a soluble colloid to a reagent which converts it into an insoluble colloid. I hold therefore that there is no evidence that the structure discoverable in the cell-substance of these cells after fixation has any counterpart in the cell when living. A large part of it is an artifact.[61]

Armed with the new language of sol-gel transformation, Hardy concluded that fixative chemicals produced a dramatic and irreversible rearrangement of the structure of all colloids — and that fixatives worked by rearranging the more fluid and more solid parts of the colloid. The resulting visible structure, in both fixed gelatin and fixed animal tissue, was thus likely foreign to the natural state of both.

Taking these two statements together, we can see that Hardy is arguing that protoplasm was a colloid or at least had many colloidal characteristics, by demonstrating that non-living colloidal matter behaves exactly the same way towards osmic acid and corrosive sublimate as does living cell protoplasm. Even though Hardy's declared target was a technique, the use of fixatives, he actually decided that the topic of his study was arguing whether protoplasm had colloidal structure. In so doing gelatin, agar, egg white, and olive oil became models, even proxies for studying living protoplasm, or life itself.

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60. *ibid.*, 203.

61. *ibid.,* 206.

e. *Conclusion*

Hardy's "On the Structure of Cell Protoplasm" was not just a remarkable work in cytology: along with its companion article, ""On the Coagulation of Proteid by Electricity," published the same year, it was a notable contribution to colloid chemical theory in general. Hardy had begun with a study of protoplasmic structure and fixation artifacts, but his work ended up showing the properties and differences between more dilute and more concentrated colloidal systems — the aforementioned precipitations of nets and granules, depending on the nature of the colloid before fixation.[62] As the next chapter will show, Hardy's article marked the beginning of a new phase of research into the nature of living matter. In this new twentieth century phase, the study of protoplasm would have just as much an impact on colloid chemistry and the physical sciences as it would in the sciences of life. After 1899, cytological techniques, or perhaps more accurately the concern about errors in cytological techniques, would push Hardy and an entire generation of cell researchers towards colloid chemistry and the physical sciences. In fact, between 1900 and his death in 1933, Hardy would only rarely revisit biological topics, and then only if they offered insight into colloid chemical theory. He would become one of the leading figures of colloid physics, an expert in lubrication and the physics of surfaces and interfaces; he will reappear in Chapter 5.

Hardy's suspicion and even outright rejection of fixatives for research into the structure of protoplasm was not new: versions of such suspicions could even be attributed to Flemming's caution towards strong and fast fixatives in 1882. Hardy's genuinely revolutionary act in "On the Structure of Cell Protoplasm" was to demonstrate that protoplasm and gelatin could be studied in exactly the same ways, including fixation, thin sectioning, and staining. Even though this practice had

62. Frederick Gowland Hopkins and FES, "William Bate Hardy, 1864-1933," 328.

originated nearly two decades earlier, for Flemming, Berthold, and Schwarz alike the appearance of the net-like coagulate was a sign of improper fixation first and foremost, rather than a major change in how they thought about what protoplasm was. Berthold and Schwarz did suggest that this phenomenon pointed to protoplasm as a coagulable emulsion, but ultimately they did not think that calling the protoplasm an "emulsion" was a sufficient argument about the protoplasm's structure. And what Fischer lacked, in retrospect, was Hardy's more sophisticated vocabulary and conceptual tools to see the coagulation beyond his very simple, dualistic categorization of "granular" and "clotted" fixation artifacts.

As the next chapter will show, protoplasm research after 1899 moved away from visual, anatomical approaches, becoming more quantitative, physicalist, and abstract — a result of Hardy and Fischer's amplified concerns about fixation techniques, Hardy's redefinition of protoplasm as a colloid, and the growing interest in applying physico-chemical methods to biology more generally. As a word of caution for the remaining chapters, however: Berthold, Schwarz, Bütschli, Fischer, and Hardy's work with homogenous, non-living substances happened at the expense of explorations into the diversity of cells and intra-cellular structures. By the 1890s questions about protoplasmic structure seemed to diverge entirely from questions of cellular morphology, especially those of nuclear and cellular multiplication. Research into protoplasm, the living matter, became a more specialized endeavor, demanding different techniques and conceptual universes than research into cellular and organismal development. The next chapter and the conclusion will try to address at the difficulties and contradictions that resulted from this situation. It was one that biologists never managed to resolve as long as they retained the idea of a unified, universal living substance.

Chapter 3: *Protoplasmatologia*: Physicalizing Life in the "Dark Age of Biocolloidology," 1899–1930

> But colloid chemists do not take the definition of their science too seriously.
>
> — Lewis Victor Heilbrunn, *The Colloid Chemistry of the Protoplasm*[1]

There were many days in 1921 when one could find the young American physiologist Lewis Victor Heilbrunn (1892–1959) sitting in the University of Michigan's zoology laboratory, carefully examining sea urchin eggs under a microscope. He would choose one of them, swiftly pipette it into a glass tube, insert the tube into a Bausch & Lomb hand-crank centrifuge, and give the single sea urchin egg a very gentle whirl, counting the seconds as they passed — between three and eighteen seconds, to be precise. Then, after braking the centrifuge: an even swifter pipetting of the lone sea urchin egg out of the glass tube and back onto the microscope slide. For the egg, the brief ordeal was now over; for Heilbrunn, he would continue to gently centrifuge sea urchin eggs for another 36 years, at a pace which he assured others was not leisurely, despite the rather slow turning of the centrifuge crank.[2] The reward for Heilbrunn's patient and determined effort was a remarkable finding: protoplasm, the material bearer of life, was about seven times as viscous as water — less than sulfuric acid, far less than olive oil.[3]

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1. L. V. Heilbrunn, *The Colloid Chemistry of Protoplasm*, Protoplasma-Monographien, Bd. 1 (Berlin: Gebrüder Borntraeger, 1928), 7.

2. L. V. Heilbrunn, "Protoplasmic Viscosity Changes during Mitosis," *Journal of Experimental Zoology* 34, no. 3 (1921): 416–47; Heilbrunn on 423 assures the reader his measurements would have been more accurate had he "had time to proceed leisurely." Elsewhere hesuggests using an electric centrifuge if hand-cranking becomes "wearisome" (see note 3, below).

3. L. V. Heilbrunn, "The Absolute Viscosity of Protoplasm," *Journal of Experimental Zoology* 44, no. 1 (April 1926): 255–78, on 267 and 273. In 1928 he revised his measurement upwards, to between seven and "something less than eleven" times that of water at 20°C, while the figures he supplies for sulfuric acid and olive oil are twenty-three and ninety-nine times the viscosity of water, respectively; L. V. Heilbrunn, *The Colloid Chemistry of Protoplasm*, 60, 79.

Heilbrunn was one of the staunchest defenders of a certain kind of colloid chemical orthodoxy that took hold within biology during the first half of the twentieth century. After William Bate Hardy's proclamation in 1899 that protoplasm was a colloid, a considerable number of biologists rushed to see what this new discipline of colloid chemistry could offer them. What they found was not a new kind of chemistry, but rather an old kind of physics that had been repackaged and rearranged to make physics more applicable to a vast range of material problems and ordinary experiences — problems that had yet to see the benefits of modern science. From its very origins in the mid-nineteenth century, colloid chemistry was a science of unruly, slimy, impure or heterogeneous materials, like gelatin, blood, rubber, glue, cement, dairy, and, after 1899, protoplasm — substances that were often not obviously pure solutions, liquids, or crystalline solids. In its early years, the whole point of colloid chemistry was to see what methods could be brought to bear to analyze substances that could not be examined using standard chemical-analytical practices.

Colloid chemistry was a science that tended to be instrumentalist or nominalist in its methods; typical experimental topics included viscosity, flow, opacity, behavior in changing temperatures, response of a colloid to mechanical forces, and response to electrical fields and charges. Colloid chemists' focus on techniques of measurement and mathematical description of materials at hand allowed them to communicate across vastly different specialties, despite working with a diverse range of colloidal materials. John Heilbron, Ted Porter and others have called this general tendency in *fin-de-siècle* physics "descriptionism."[4] Porter in particular has argued that this epistemological remove from specific objects of inquiry allowed physics to broaden its scope and cultural influence — that "descriptionism aimed to make physics almost impregnable, to confer on it

4. John L. Heilbron, "Fin-De-Siècle Physics," in *Science, Technology, and Society in the Time of Alfred Nobel*, ed. Carl Gustaf Bernhard, Elisabeth Crawford, and Per Sörbom (Oxford: Nobel Foundation, 1982), 51–73; and Theodore M. Porter, "The Death of the Object: Fin de Siècle Philosophy of Physics," in *Modernist Impulses in the Human Sciences, 1870-1930*, ed. Dorothy Ross (Baltimore: Johns Hopkins University Press, 1994), 128–51. See also Richard Staley, "The Fin de Siècle Thesis," *Berichte Zur Wissenschaftsgeschichte* 31, no. 4 (December 2008): 311–30.

something like the degree of certainty normally associated with mathematics…the release of physics from all particular objects helped to dissolve the boundaries that confined physics to one aspect of the natural world."[5] This would certainly apply to colloid chemists' repeated insistance that the definition of "colloids" was a relative and relational matter, rather than an issue of absolute and logically rigorous definition. The diversity of topics in colloid chemistry journals, symposia, and international meetings meant that publishing in *Kolloid-Zeitschrift* or *Protoplasma*, or attending a meeting of the Faraday Society, gave an individual scientist potentially broad reach.[6] In its heyday in the 1920s and '30s, colloid chemistry became a kind of super- or inter-discipline, an intellectual space where cell physiologists could comfortably communicate with metallurgists, sewage engineers, or soap chemists.

But what did colloid chemistry bring to biology after 1899, and what did colloid chemistry bring to protoplasm theory? This chapter will argue that biologists' reconceptualization of protoplasm as a colloid opened new avenues for the physicalization of biology — an unintuitive claim if one gives the "chemistry" part of "colloid chemistry" too much emphasis. The specific kind of physics colloid chemists embraced was grounded in thermodynamics and energy physics, with a preference for quantification and measurement of material phenomena over and above microphysical hypotheses about the structure of matter. While almost no colloid chemists would have argued that atoms and molecules were merely fictions, in practice and vocabulary colloids were treated as continuous matter, and when colloid chemists did examine particles or molecules it was done so in probabilistic or aggregate ways. This makes colloid chemistry something of an historical puzzle: the period 1900–1930 was exactly when the biological and physical sciences seemed to be moving

5. Theodore M. Porter, "The Death of the Object," 130.

6. In fact the Faraday Society meetings not only often featured international guests, but the proceedings were often translated and published in German in *Kolloid-Zeitschrift*; for example, the 1913 discussion on "Colloids and their Viscosity" in London, *Transactions of the Faraday Society* 9, 34–107, and *Kolloid-Zeitschrift* 12, no. 5, 213–263.

towards discontinuity: the early twentieth century saw the development of genetics, evolutionary theory, quantum theory, and physical atomic theory, all of which privileged the discrete over the continuous. "Continuity and discontinuity," writes the historian Everett Mendelsohn, "are not constructs of nature but constructs of the human mind used to interpret nature. It is the observer and the interpreter of the physical world who posit continuities and discontinuities in the materials before them."[7]

Colloid chemistry more generally, as this chapter will show, was a science that was caught between physicists' desire to focus on insights gained by practical, tactile manipulation of everyday materials, and an imperative to think of those same materials by means of mathematical abstractions. What biologists would find most problematic by the 1930s was that colloid chemistry's intensely positivist and descriptivist approach had only a little room for visual studies, and was therefore poorly suited for what most biologists were trained to be good at: visual identification and distinction among species, organisms, and anatomical objects. Colloid chemistry might have been a perfect way to study protoplasm; it could be an awful way to study cells.

Put another way, this chapter will try to answer the question: *Why* was Heilbrunn spending so much time gently centrifuging sea urchin and other marine animal eggs? Nobody doubted Heilbrunn had made an accurate measurement; exactly *what* he had measured was a topic of considerable debate. The physicist Frederick Donnan (1870–1956) argued that Heilbrunn had done no less than solve the entire problem of the structure of protoplasm: protoplasm had no structure. In the middle of a conversation in 1930 about the possible existence of a cell cytoskeleton, Donnan objected, pointing to the fact that,

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7. Everett Mendelsohn, "The Continuous and the Discrete in the History of Science," in *Constancy and Change in Human Development*, ed. Orville G. Brim, Jr. and Jerome Kagan (Cambridge: Harvard University Press, 1980), 75–112, on 107.

> The careful and extensive measurements of L. V. Heilbrunn showed that the viscosity of living cytoplasm was relatively low and did not exhibit any variation with rate of shear. It would appear, therefore, that the living cytoplasm did not possess any structural elasticity. It might, of course, be possible that the cytoplasm was a very delicate thixotropic gel (one whose viscosity decreases with applied stress or agitation) whose internal structure was easily broken down by the moving granules in Heilbrunn's experiments. Would such a system show a measurable variation of viscosity with variation of rate of shear? What was the relaxation time of such a system? Even were the living cytoplasm proved to be a very delicate thixotropic gel, it was difficult to imagine how such a system could provide for a spatial arrangement and segregation of chemically reactive substances.[8]

In some ways, this chapter's job is to unpack Heilbrunn's research and Donnan's response to it — to find the disciplinary and scientific contexts in which the question, "What is the viscosity of protoplasm?" was intelligible, let alone answerable.[9]

This chapter will show some the contours of Heilbrunn and Donnan's scientific community by excavating the strange metaphysics of colloid chemical biology. The first part of this chapter will look at colloid chemists' attempts to define what a colloid is, and how the definition of "colloid" shaped the disciplinary scope of colloid chemistry. The second section will look at the reconceptualization of protoplasm as a colloid after 1899, and the establishment in the 1920s of a kind of "protoplasm studies" that emphasized measurement and quantification of protoplasmic and cellular phenomena. This section will build up to the 1930 meeting of the Faraday Society, organized around the topic "Colloid Science Applied to Biology," where Donnan made his aforementioned remarks.

This chapter concludes with a look at the historiography of colloid chemistry in biology. There are three reasons for this. First, the historiography of colloid chemistry in biology tends to focus on a particular, whiggish historical trajectory, "from colloids to macromolecules," which

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8. General discussion to Rudolph Albert Peters, "Surface Structure in the Integration of Cell Activity," *Transactions of the Faraday Society* 26 (1930): 815–16. This is a lightly summarized conference transcript, hence the odd grammar.

9. "The questions real in a community," philosopher Nicholas Jardine has suggested, "are the questions for which there exist considerations that would be acknowledged in the community as providing grounds for preferring one full and direct answer over all the others. Nicholas Jardine, *The Scenes of Inquiry: On the Reality of Questions in the Sciences* (Oxford: Clarendon Press, 1991), 4.

emphasizes either the overcoming or the decline of colloid chemistry in the 1930s and '40s. Since the following two chapters are closer to this later period, it makes somewhat better narrative sense to leave the historiographical discussion towards the end of this present chapter. Second, I wish to suggest that the idea colloid chemistry "declined" in the first place was itself an artifact of this historiography: as this and the following chapters will hopefully show, "colloids" and "molecules" are not incommensurable in the Kuhnian sense. Rather, this historiography is a reflection of a shift in the kind of biophysics that arose after the Second World War, as well as the dramatic changes in biochemistry that the new biophysics helped legitimize. Finally, I want to gesture toward some of the historical differences between colloid chemical biology and biochemistry, the latter of which is more familiar to us today. The science in these first sections will seem far stranger, and more buried in the detritus of the past.

a. Positivism and the history of colloid chemistry

In the winter of 1913, Wolfgang Ostwald (1883–1943), son of the far more famous physical chemist Wilhelm Ostwald, embarked on the scientific equivalent of a tent revival tour, giving fifty-six lectures at twelve different North American universities and scientific societies from Montreal to Oklahoma.[10] The gospel the younger Ostwald proclaimed was colloid chemistry, and his American audiences seem to have converted in droves. John Servos has tabulated the explosive growth in colloid chemistry articles in the *Journal of the American Chemical Society* rising from just 4% of all *JACS* articles in 1909–13, to 14% in 1914–18, and 19% 1919–23; Andrew Ede has shown that by 1935 most North American graduate students in chemistry could take advanced courses in colloid

10. Wolfgang Ostwald, *An Introduction to Theoretical and Applied Colloid Chemistry, "The World of Neglected Dimensions,"* trans. Martin Fischer, 1st ed. (New York: John Wiley & Sons, 1917), *ix*.

chemistry, and sixteen North American chemistry programs made colloid chemistry courses compulsory.[11] The first lecture of his five-lecture sequence was entirely devoted to the question: "What are colloids?" and the question took Ostwald a remarkably long time to answer. What he did first was display a series of prepared colloids while describing their appearance and properties, and he may even have prepared some of them on the stage. In the script of the lecture, published in English during the war, Ostwald began the lecture series by displaying colloidal preparations of mercury chromate, Prussian blue, silicic acid, gelatin, agar, starch, gum arabic, india ink, colloidal gold, even an odd preparation of colloidal sodium chloride.[12] Ostwald was drawing on a strong tradition of theatrical science demonstrations, and that precedent was not only the entertainment value of popular science lectures: demonstrations of exemplary colloidal materials were a feature of the history, lore, and the definition of what colloid chemistry was.[13] It was far easier to show prototypical exemplars of colloids than to try to define colloids using a logical classification scheme.[14] And while textbooks could not offer entertaining, live demonstrations, they often included rich verbal descriptions of the texture, behavior, and tactile qualities of select colloids. Richard Zsigmondy (1865–1929) even began his Nobel Prize lecture by reflecting that, "Even in prehistoric times the peoples must have become familiar with the properties of colloidal solutions and with their changes. The curdling of milk and the clotting of blood were certainly known to our oldest ancestors."[15]

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11. John W. Servos, *Physical Chemistry from Ostwald to Pauling: The Making of a Science in America* (Princeton: Princeton University Press, 1990), 385ff; Andrew Ede, *The Rise and Decline of Colloid Science in North America, 1900-1935: The Neglected Dimension* (Burlington: Ashgate, 2007), 78–83. Servos' survey of the *JACS* is of its general and physical section.

12. Wolfgang Ostwald, *An Introduction to Theoretical and Applied Colloid Chemistry*, 5–6.

13. On theatrical science performances in the nineteenth century, see Iwan Rhys Morus, "Seeing and Believing Science," *Isis* 97, no. 1 (March 2006): 101–10.

14. On categorization and prototyping effects, see George Lakoff, *Women, Fire, and Dangerous Things: What Categories Reveal about the Mind* (Chicago: University of Chicago Press, 1987).

15. Richard A. Zsigmondy, "Nobel Lecture: Properties of Colloids (1926)," in *Nobel Lectures, Chemistry 1922–1941* (Amsterdam: Elsevier, 1966), 45–57.

A second, even more common way of explaining colloids did not require reaching so deep into pre-history. Wilder Bancroft's *Applied Colloid Chemistry: General Theory* began with the origin of the word "colloid" and the history of the discipline: "In 1861, Graham pointed out that substances like potassium hydroxide, potassium sulphate, magnesium sulphate, sugar, and alcohol diffuse much more rapidly in water than hydrous silicic acid, hydrous alumina, starch, dextrin, the gums, albumin, tannin, gelatine, etc."[16] In fact this was the Scottish chemist Thomas Graham's (1805–1869) own list, from his 1861 *Philosophical Transactions* article where he had coined the term "colloid" to describe these gelatinous substances.[17] Graham had also provided other key definitions for what he repeatedly referred to as "the colloidal condition of matter": colloids did not seem to crystallize using chemists' normal procedures, and they resisted diffusion through parchment paper. From here, Graham had divided colloids into two categories: sols, colloids that had a more fluid consistency, and gels, evaporated sols that seemed more like set gelatin.

Thus, from the very beginning, "colloids" were somewhat loosely defined through a comparison with a few exemplary cases of the "colloidal condition," usually using fairly large-scale samples. This was reinforced through earlier definitions of colloids that were strictly procedural: Graham's 1861 parchment paper filter, for instance, used "a sheet of very thin and well-sized letter paper, of French manufacture" held in place by rubber rings in a five-inch deep jar.[18] This lack of a clear, formal definition of both colloids and of colloid chemistry persisted well into the twentieth century. The Swedish colloid chemist Theodor "The" Svedberg (1884–1971) echoed this common inductivist theme, telling students at the University of Wisconsin in the spring of 1923 that for the

16. Wilder D. Bancroft, *Applied Colloid Chemistry: General Theory* (New York: McGraw-Hill, 1921), 1.

17. Thomas Graham, "Liquid Diffusion Applied to Analysis," *Philosophical Transactions* 151 (1861): 183–224. Later writers added the etymology, "*κολλα*," the Greek word for glue.

18. *ibid.,* 185.

discipline, "the great difficulty is to find out general laws governing the behaviour of colloids; hence the study of the different colloid systems must precede the formation of general laws."[19]

A flurry of schemes for classifying colloids appeared in the first decade of the twentieth century; these initial attempts distinguished colloids from non-colloids, and divided up the world of non-homogenous materials by their behaviors, reactions, or structure. Besides establishing the original distinction between colloids and crystalloids, Graham in 1861 had divided colloids into two categories: sols, colloids that had a more fluid consistency, and gels, evaporated sols that seemed more like set gelatin (hence the term). Graham's two-part classification stood until a flurry of different classification schemes appeared around the beginning of the twentieth century. In 1899, W. B. Hardy, while trying to establish the connection between protoplasm and colloids (see Chapter 2), found that some physical coagulations of agar and gelatin (*e.g.*, by heat or evaporation) could be reversed by heating, while some chemical coagulations (*e.g.,* coagulations caused by many fixatives) were irreversible.[20] In 1903, Richard Zsigmondy (1865–1929) was the first to argue that Graham's distinction between pure solutions and colloids was a difference of degree rather than kind — that "no sharp line of demarcation can be drawn between suspensions and colloidal solutions; their spheres mutually invade each other" (Figures 3.2 and 3.3).[21] In 1907, Wolfgang Ostwald argued, from the basis of Zsigmondy's work on colloidal particles, that colloids were fundamentally heterogeneous dispersions or "disperse systems," consisting of particles in a disperse phase within a dispersion medium.[22]

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19. Theodor Svedberg, *Colloid Chemistry: Wisconsin Lectures* (New York: Chemical Catalog Company, 1924), 12.

20. W. B. Hardy, "On the Structure of Cell Protoplasm," *The Journal of Physiology* 24, no. 2 (May 11, 1899): 158–210; the irreversibility of coagulations caused by fixative chemicals is what led Hardy to condemn their use in cytology.

21. Richard Zsigmondy, *Colloids and the Ultramicroscope: A Manual of Colloid Chemistry and Ultramicroscopy*, trans. Jerome Alexander (New York: John Wiley & Sons, 1909), 26. On the ultramicroscope and Zsigmondy's work in colloid cheimstry, see David Cahan, "The Zeiss Werke and the Ultramicroscope: The Creation of a Scientific Instrument in Context," in *Scientific Credibility and Technical Standards in 19th and Early 20th Century Germany and Britain*, ed. Jed Z. Buchwald (Dordrecht: Kluwer, 1996), 67–115.

22. Wolfgang Ostwald, "Zur Systematik der Kolloide," *Zeitschrift für Chemie und Industrie der Kolloide* 1, no. 10 (April

		DISPERSE/ PARTICLE **gas**	**liquid**	**solid**
DISPERSION MEDIUM/ CONTINUOUS PHASE	**gas**	– –	*mist, aerosols*	*smoke*
	liquid	*foam*	*emulsion, sol, gel*	*suspension, sol, gel*
	solid	*solid foam*	*solid emulsion*	*solid suspension*

Finally, one of the most important of these early projects to define the colloid state was Herbert Freundlich's (1880–1941) generalization of Ostwald's dispersion theory in 1909: Freundlich translated the disperse structure of colloids in terms of surface structure, arguing that a colloid's overall structure and behavior is a product of each colloidal particle's interaction with its disperse medium (Figure 3.4).

The most important of these refinements to the definition of colloids were centered around Zsigmondy and Henry Siedentopf's (1872–1940) invention of the slit-ultramicroscope in 1903. The ultramicroscope allowed Zsigmondy to show that all colloidal sols consisted of particles suspended in a continuous fluid medium. Crucially, it also allowed scientists to measure colloidal particles' size and color (Figure 3.1). By the 1880s, physicists had determined theoretically that the smallest object that could be resolved by a light microscope could be no smaller than half the wavelength of light. Zsigmondy and Siedentopf's ultramicroscope was able to overcome this physical limit by illuminating a sample perpendicular to the microscope objective; the viewer would see spots of light diffracting off of the colloidal particles. It was possible, if "difficult and laborious," to quantify the frequency and distribution of the colloidal particles.[23] With effort, however, ultramicroscopy became

1907): 291–300. This table is adapted from Wolfgang Ostwald, *An Introduction to Theoretical and Applied Colloid Chemistry*, 42.

23. David Cahan, "The Zeiss Werke and the Ultramicroscope,"

one of the most reliable ways for relating the dispersion (*i.e.,* number, distribution, and size) of colloidal particles to the bulk mechanical, structural, and optical properties of the whole colloid.

The appearance of Zsigmondy and Siedentopf's ultramicroscope marked "a psychological turning point" in the history of colloid chemistry.[24] It was one of the earliest tools for the optical study of colloids; it offered proof both that colloids were disperse structures, and that solutions, colloids, and mechanical suspensions lie on a spectrum of kinds of disperse structures. All of the variations on colloidal classification after Zsigmondy's emphasized that there were no clear logical or empirical distinctions between colloids and crystalloids, and that such differences were merely conventional. One common refrain from colloid theorists was an insistence that the word "colloid" was better used as an adjective to describe the way multiple materials interacted rather than as a single kind of matter: that "it is in general more exact to speak of colloidal systems than of colloidal substances, and to understand by the term 'colloid' a colloidal system."[25] In 1917, as he showed off his preparations of gelatin and Prussian blue, Ostwald was at pains to remind his American audiences that "modern colloid chemistry teaches that there are no sharp differences between mechanical suspensions (*e.g.,* particles kept aloft in a fluid by stirring), colloid solutions, and molecular solutions. There is a gradual transition from the first through the second to the third."[26]

Within a few years of its invention, the ultramicroscope would allow colloid chemistry to become tied with the kinetic theory in physics, along with the gas law, the law of solutions, and Albert Einstein's theory of the atomicity of matter. Zsigmondy wrote that in 1905 he was shocked to find that the colloidal particles he observed exhibited Brownian motion, the ceaseless, random jumping and vibration of tiny particles first observed by the botanist Robert Brown in 1826. As

24. James W. McBain, *Colloid Science* (Boston: D.C., Heath, & co., 1950), 11.

25. Richard Zsigmondy, "Kolloidchemie," in *The Chemistry of Colloids*, trans. Ellwood Barker Spear (New York: John Wiley & Sons, 1917), 4.

26. Wolfgang Ostwald, *An Introduction to Theoretical and Applied Colloid Chemistry*, 14.

David Cahan has recounted in his history of the ultramicroscope, from 1905 to 1908 Einstein had produced a theoretical approach that described the movement of a single spherical molecule in a fluid, making the then-unproven assumption that fluids obeyed the same molecular kinetics as did gasses.[27] Jean Perrin's experimental demonstration of the Einstein-Smoluchowski relation in 1909 was definitive proof to even the most intransigent of physicists that matter was fundamentally discontinuous and made of discrete atoms and molecules.[28]

The proof of the atomicity and fundamental discontinuity of matter was not, however, the end of the story for colloidal particles. Ironically, colloid chemists exploited the ultramicroscope and kinetic theory to *ignore* atomic theory, and to emphasize the continuity of physical phenomena like surface tension, heat capacity, and viscosity. One of the major theoretical projects in colloid chemistry attempted to relate the total surface area within a disperse system: if each colloidal particle was conceived as being in surface contact with the fluid medium, then the total surface area within a hypothetical $1cm^3$ colloidal system might be measurable square kilometers.[29] This will be discussed in greater detail in Chapter 5, but briefly for now: this internal surface could be a site of adsorption, catalysis, aggregation, friction, pressure, electrical charge, and, of course, movement in the form of Brownian motion. In 1909, Freundlich developed a thorough reinterpretation of surface phenomena from the perspective of thermodynamic "free energy": generally speaking, this meant that a stable colloid possessed a certain amount of energy that resisted outside forces, *e.g.* a resistance to

27. David Cahan, "The Zeiss Werke and the Ultramicroscope," 101-102. The technical and mathematical details of the debate are thoroughly discussed in Mary Jo Nye, *Molecular Reality: A Perspective on the Scientific Work of Jean Perrin.* (London: Macdonald, 1972), chapter 3.

28. Mary Jo Nye, *Molecular Reality*; on Perrin's work with the ultramicroscope and colloidal gamboge, see Charlotte Bigg, "Evident Atoms: Visuality in Jean Perrin's Brownian Motion Research," *Studies in History and Philosophy of Science Part A* 39, no. 3 (September 2008): 312–22; and "A Visual History of Jean Perrin's Brownian Motion Curves," in *Histories of Scientific Observation*, ed. Lorraine Daston and Elizabeth Lunbeck (Chicago: University of Chicago Press, 2011), 156–79,

29. James W. McBain, *Colloid Science*, 7.

sedimentation by the force of gravity.[30] Any significant transformation, such as a change in viscosity, or an irreversible precipitation of a sol into a gel, could then be interpreted and analyzed as a change in the amount of energy possessed by the colloidal system; this would be measurable and quantifiable by analyzing changes in temperature, volume, etc.

With the exception of the ultramicroscope for determining colloidal particle size and dispersion, for the most part colloid chemists relied on physical methods of measurement that worked on bulk, material systems. For example, one type of instrument used to measure surface tension worked by placing a thin metal disk on the surface of a fluid, and measuring how much weight was required to lift the disk off of the surface. Another used photographic images of jets of fluids pumped through a thin aperture, the surface tension determined by measuring wavelength of the fluid jet's oscillations in three dimensions.[31] Viscometry readings could made by dropping a spherical ball through a column of the liquid or colloid and measuring its velocity and acceleration; other methods included measuring the force required to stir a colloid, or letting a particularly viscous colloid form droplets. One famous example of the latter is the so-called pitch drop experiment at the University of Queensland that began in 1927 and still runs today, in which seemingly solid pitch held in a funnel actually flows and produces large drops at the rate of about once per decade.[32]

Richard Staley has recently argued that descriptivism and positivism were alive and well in theoretical physics immediately around the turn of the twentieth century, and he has also suggested that descriptivism might be connected to Weimar-era physics' tendency toward acausal forms of

30. Herbert Freundlich, *Kapillarchemie: Eine Darstellung der Chemie der Kolloide und verwandter Gebiete* (Leipzig: Akademische Verlagsgesellschaft, 1909); an English translation of the third German edition (1923) is Herbert Freundlich, *Colloid & Capillary Chemistry*, trans. H. Stafford Hatfield (London: Methuen & co. ltd., 1926.

31. Herbert Freundlich, *Colloid & Capillary Chemistry*, 12–13.

32. http://smp.uq.edu.au/content/pitch-drop-experiment

argument and physical reasoning.[33] The very brief history of colloid chemistry above has tried to highlight some of the same positivist tendencies in what might best be considered a vibrant area of applied physics. Colloid theorists in the 1920s worked both to dramatically expand the range of materials they could bring under the new discipline, as well as to intensify the mathematical physics (in both thermodynamics and kinetics) that held the whole endeavor together — the 1922 edition of Freundlich's *Kapillarchemie* is almost unreadable to someone not trained in mathematical physics. As the next section will show, biologists adopting colloid chemistry for the first time in the 1910s and '20s were not often equipped to work with the mathematics at Freundlich's level, but they did adopt some of the spirit of positivism and quantification as they explored protoplasm with these new methods.

b. Protoplasm studies in the early twentieth century

In 1899 Hardy had argued that colloid chemical terminology could be helpful in describing the structure of protoplasm, particularly the language of sol-gel transformations. This ambition was greatly frustrated in 1905–1910, when the Russian botanist Nikolai Mikhailovich Gaidukov (1874–1928) visited the Carl Zeiss optical works in Jena, and began to use Zsigmondy and Siedentopf's new ultramicroscope to look at plant cells.[34] Gaidukov reported that in several types of algal cells, notably *Spirogyra*, he could clearly see colloidal particles exhibiting Brownian motion, suggesting that protoplasm was a "complex hydrosol." In the same cells, however, the outer area of the protoplast, *i.e.* closest to the cell wall and cell sap, these were cloudier, more gel-like. In a few other algal species Gaidukov saw no Brownian motion, and sometimes no particles at all — they were

33. Richard Staley, "The Fin de Siècle Thesis."

34. "Gaidukov, Nikolai Mikhailovich. (n.d.)," *The Great Soviet Encyclopedia*, 3rd ed. translation, (New York: Macmillan, 1975), vol. 6, 37c/6-132-1. For more on the Zeiss optical works and scientific microscopy at Jena see Chapter 4.

"optically empty" ("*optisch leer*").[35] There was no clear correlation between vital activity, the presence or absence of colloidal particles, or the presence or absence of Brownian motion in the same. Gaidukov could only argue that protoplasm had two parts: an inner hydrosol that showed Brownian motion, and an outer "hydrogel layer" ("*hydrogelschicht*") that was optically empty. He suggested that this hydrogel layer might be a protective layer, which previous investigators called either the hyaloplasm or the ectoplasm. If this was the case, it might be produced by the active protoplasmic hydrosol coming into contact with electrolytes in both the central vacuole and the cell's outer environment. Gaidukov was thus able to argue that protoplasm was "polymorphic," but he was otherwise unable to make much more of his investigations using the ultramicroscope.

While ultramicroscopy became an essential tool in colloid chemistry more broadly, biologists grew wary of the difficult preparation techniques, the inherently fraught nature of using indirect illumination on a complex, often membrane-bound object; in addition, the ultramicroscope could not be used on any cells containing larger granules, vacuoles, or other bodies, since they would appear very luminous and obscure the smaller colloidal particles. "It may perhaps be said that the method has not realised to the full, the expectations of those who hoped it would clear up definitely certain vexed questions of cell structure," wrote one of Gaidukov's reviewers.[36] In fact, the inconclusive results by Gaidukov and other ultramicroscopic investigations only exacerbated the feelings from the 1890s that a theory of protoplasmic structure was growing more remote. "With great enthusiasm biologists mastered the new method," the Swiss botanist Albert Frey-Wyssling wrote in 1938, "but [they] discovered with disappointment that nearly all important biological objects:

35. Nikolai Gaidukov, *Dunkelfeldbeleuchtung und ultramikroskopie in der biologie und in der medizin* (Jena: Gustav Fischer, 1910), 60–66; the English botanist S. Reginald Price extensively summarized and reviewed Gaidukov's work in "The Method of Dark-Ground Illumination in Botanical Research," *Science Progress* 8, no. 30 (1913): 343–54; and, "Some Studies on the Structure of the Plant Cell by the Method of Dark-Ground Illumination," *Annals of Botany*, no. 4 (1914): 601–32.

36. S. Reginald Price, "The Method of Dark-Ground Illumination in Botanical Research," 353.

cytoplasm, nuclei, plastids, cell walls, etc., are 'optically empty.'"[37] Frey-Wyssling was not strictly correct: Gaidukov had seen *something.* But he was not able to see enough, and Frey-Wyssling could have written instead that Gaidukov *might as well* have not seen anything.

Rather than continue to examine protoplasm's discrete colloidal particles, biologists took Gaidukov's cue and began to think of it as a continuous, aggregate whole. Colloid chemistry now left biologists two ways to think of protoplasm: one was to continue to use the language of sol-gel transformations, and to think of protoplasm (in admittedly vague terms) as a polymorphic colloidal system; the other was to look for quantitative approaches to explain-away or to work around protoplasm's optical emptiness.

Much of the writing on protoplasm tended to fall in the former category until the mid-1920s; in fact, there was a minor boom stretching through the 1930s in speculative articles that tried to synthesize or promote the latest research — often with the title, "The Structure of Protoplasm," or, "The Physical Basis of Life." In January 1916, Hardy took a break from his work on a general theory of colloids to lecture on "Some Problems of Living Matter," about which he said, "There is no lack of such problems. I am embarrassed by their number and variety."[38] Hardy seemed quite ready and willing to compare a wide range of cell-physiological phenomena to behaviors observed in simple, non-living colloids, and a list of those physiological phenomena reads like the table of contents of a physiology textbook. The following table is be extrapolated from Hardy's text:

Physiological phenomenon	*Comparison to colloidal phenomena*
amoeboid movement	electric contact potential difference; gel rolling off an incline plane

37. Albert Frey-Wyssling, *Submikroskopische Morphologie des Protoplasmas und seiner Derivate*, Protoplasma-Monographien, bd. 15 (Berlin: Gebrüder Borntraeger, 1938), 3; translation from Albert Frey-Wyssling, *Submicroscopic Morphology of Protoplasm*, trans. Mary Hollander, 2nd English ed. (Amsterdam: Elsevier, 1953), 4.

38. W. B. Hardy, "Some Problems of Living Matter," *Proceedings of the Physical Society of London* 28, no. 1 (1915): 99–118, on 99.

oxidative processes	surface contact reaction
directive growth	diffusion column
nutrition, vitamins	action of colloidal electrolytes
death	irreversible gelation; suppression of Brownian movement; decrease in free energy corresponding to increase in temperature
rate of growth	particle saturation/supersaturation point
nerve impulse	??? [39]
contractile movement	sol-gel precipitation; annealing glass
selective permeability	osmotic pressure, electric endosmose gradient potential
spontaneous change	vibration of a drop of mercury in dilute chromic acid

Hardy was worried all of these activities had to be associated with "an optically homogenous substance, in which are embedded a multitude of minute particles," and that "the material basis of life is apparently much less structural than, for instance, a simple gel" — the kinds of gels that he had worked with in 1899.[40] The only distinct element of "structure" he could work with were the multitude of colloidal particles.

In order to make sense of what he knew about cellular physiology and protoplasm's seeming lack of structure, Hardy turned to abstract molecular forces as a way out, trying his best to connect the motion and arrangement of protoplasm's colloidal particles to the organism's energy intake or output.

39. Hardy argues that nerve impulses are due to both energy changes and to an oxidative chemical change, but that the chemical change "is one of exceptional character" and with a very low temperature coefficient; W. B. Hardy, "Some Problems of Living Matter," 113.

40. *ibid.*, 99–100.

> The colloid particles maintain their independence, but their relation to each other and to the continuous medium are changed in such a way as to make their potential energy a function of their position. The molecular mechanism of these changes is quite obscure. We may picture to ourselves the colloid particles as strain centres — the microscope justifies so much — and the continuous medium as having the mechanical properties of an unannealed glass.[41]

Elsewhere Hardy referred to the "asymmetric field of force" that a colloidal particle might have upon the continuous medium, augmented by the kinetic energy of the whatever Brownian motion that colloidal particle might exhibit.[42] These hypothetical fields of force would then be greatly affected by the cell's electrolytic environment, which the cell's protoplasm would be constantly trying to self-regulate. "I think a certain broad conclusion is forced on us," Hardy argued, "Since electrolytes control the configuration of colloidal systems in respect to the size, number and distribution of the colloid particles, and also shape the path of change of energy in living matter, we may infer that the functional processes of a cell are conditioned by the by the configuration of the colloid," namely the way the protoplasm distributes simple salts and other electrolytic substances.[43]

While Hardy and other physiologists (and ex-physiologists) found colloid chemical language useful for explaining physiological processes, other biologists saw colloid chemistry as a way of reforming approaches to cellular anatomy, and as a way of bridging the gap between physiology and morphology. The American botanist Robert Almer Harper (1862-1946) took up this theme at the end of 1917, delivering an address on the structure of protoplasm as the outgoing president of the American Botanical Society.[44] His own research had been in the morphology and cytology of fungi and slime molds, but by the 1920s he could be heard arguing that cytology needed to become more physiological and more attuned to how cells respond to their environments.[45]

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41. *ibid.,* 109.
42. *ibid.,* 111.
43. *ibid.*, 109.
44. R. A. Harper, "The Structure of Protoplasm," *American Journal of Botany* 6, no. 7 (July 1919): 273–300.
45. R. A. Harper, "Cytology and Agronomy," *Journal of the American Society of Agronomy* 16 (1924): 595–607.

Harper's perspective on protoplasm illustrates how disruptive colloid chemical ontology and ideas of matter could be if imported into cytology — a disruption for which Harper was quite enthusiastic. Repeating the now-common line that protoplasm was a "polyphase, colloidal system," Harper began with a basic definition of cell as a unit of protoplasm:

> I shall use the term *protoplasm* as referring broadly to the whole sum of materials which make up the cell, including the cell wall, metaplasm, starch, fat, cell sap, even inorganic crystals and water of inclusion, [but] nothing is farther from my intention than to give a definition of protoplasm. Protoplasm is in most intimate relations of interchange with its environment, and, further, there is surely no hard and fast line between its external environment and its so-called internal environment…With this understanding as to definitions, I shall use the word *cell* as referring to the whole protoplasmic unit, including the wall or envelopes of every kind.[46]

The colloidal idea of interacting phases and systems also gave Harper a new understanding of organelles and plastids. For example, the irregular outlines of chloroplasts in algae such as *Spirogyra* now made more sense if they were not conceived of as bounded objects but rather regions of physiological activity: "That the plastid is to be regarded as a region of the protoplasmic complex rather than as a differentiated and definitely delimited body is shown with especial clearness in the case of those algae whose chloroplasts are of irregularly lobed or frayed-out outlines." Thus, rather than think of chloroplasts as bounded, anatomical objects, Harper argued that was better to think of them as sites of starch-assimilating activity — an explanation that might better capture the diversity of forms chloroplasts could take in algae. "The functions of the chloroplast in forming assimilation starch are strictly dependent on the presence in it of green chlorophyl, and cytologically the chloroplast is perhaps little more than an area of the cytoplasm impregnated or infiltrated with chlorophyl."[47]

For Harper, colloid chemistry was also an answer to critics who argued that biology needed to be more reductionistic methodologically and ontologically, because colloid chemistry seemed to

46. R.A. Harper, "The Structure of Protoplasm," 276-77.
47. *ibid.,* 279.

explain biological phenomena better than any chemical or physicalist language that had come before. For example, Harper argued that, "To say that the chromosomes go into solution in the telophases and reappear as crystals in the prophases was palpably absurd, but to describe the change as the passage of a gel into the continuous phase of a sol and its reverse is a chemical equivalent for many descriptions of the breaking up of the chromosomes in the telophases and their reconstitution in the prophases as found in current cytological literature."[48] The colloid chemical explanation made far more intuitive sense to Harper because chromosomes seemed like soft bodies that maintained some integrity in all phases in the cell's life, rather than dissolving into the protoplasm in fashion analogous to the way salt dissolves in water. What's more, Harper could even imagine a kind of colloidal-evolutionary history of chromosome, where a localized physiological activity begins to imprint itself (in a quasi-Lamarckian fashion?) on regions of the undifferentiated protoplasmic colloid:

> I think we may say that the chromosomes are each regions or portions of the protoplasm which by reason of the localization and specialization of certain functions and processes in them have come in some degree as has the cell itself to have a permanent unity and identity, and to arise only by the division of parent chromosomes. The protoplasm is not an aggregate of such bodies, but its activities have been specialized and localized until such bodies as chromosomes have resulted. As a polyphase colloidal system it has furnished the internal condition for the development of the greater and greater differentiation, specificity, and fixity of its phases.[49]

Harper may have been over-enthusiastic with his reconceptualization of protoplasm and the cell, chromosomes, and every other part of microscopic anatomy. Yet it was also in line with a broader movement to think about both living and non-living matter as dynamic systems — reminiscent of Cuvier's vortices from a century before — activities rather than as solid, clearly demarcated objects.

These kinds of grandiose proclamations gave way to stronger empirical work in colloidal biology in the 1920s, but the instrumentalist, positivist attitudes remained. One of the most

48. *ibid.*, 288–89.

49. *ibid.,* 285.

interesting examples of this new experimentalism in physiology was the American plant physiologist D. T. MacDougal's (1865–1958) work to build artificial cells. An outstanding problem in plant physiology since the 1870s had been protoplasm's selective permeability, *i.e.* the plant's ability to permit water and certain dissolved substances into the cell while preventing important materials from streaming out if the cell sap. In plant physiology the selective permeability of cells was crucial for understanding root action and the transport of water and nutrients within the whole plant. MacDougal's artificial, colloidal cell was built around a paper thimble, coated in what MacDougal thought were materials similar to that of protoplasm (Figure 3.5):

> The mesh of the cellulose wall is impregnated with 5 p. ct. solution of agar at 90°C, which may or may not be hardened in alcohol. The second step in the treatment consists in dipping the shell in a 10 p. ct. solution of pectin from lemons to place this material in the outre part of the wall as it the root hair.…an inner plasmatic layers [consist] of agar and gelatine of agar and proteins…[50]

After constructing the artificial cell, MacDougal immersed it in varying solutions of water, electrolytes, sugars, etc., and measured the osmotic pressure building in the middle of the cell, the simulated "cell sap." Using this apparatus, MacDougal hoped to be able to determine what role each part of the artificial plant cell played in diffusion: in one series of experiments he found that the lipoids (or fats) worked to slow the overall rate of diffusion, but they also kept salts contained inside the cell and thus increased the initial rate of "growth" as measured by the increased osmotic pressure.[51] Just as interesting historically however, is that MacDougal created one of the only schematic images of bio-colloidal system (Figure 3.6) to accompany his written reports. The assumption that the function of selective diffusion was understood as a system translated into a second assumption, also grounded in colloid theory: because the cell system (*i.e.,* the protoplasm, cell

50. D. T. MacDougal and Vladimir Moravek, "The Activities of a Constructed Colloidal Cell," *Protoplasma* 2, no. 1 (1927): 161–87, on 166.

51. D. T. MacDougal, "The Probable Action of Lipoids in Growth," *Proceedings of the American Philosophical Society* 61, no. 1 (January 1922): 33–52.

wall, and lipoidal membrane) did not function as three separate entities, they were also, anatomically speaking, not three separate entities.

Lewis Victor Heilbrunn had little patience for MacDougal's artificial cell: to Heilbrunn anything that was not direct observation of living cells was a waste of time and effort, and neither did he have patience with the kind of analogizing that Hardy had tried out in 1915.[52] Heilbrunn's extensive viscosity measurements were his way of exploring the structure of protoplasm without resorting to any measures that might alter the "normal" structure of protoplasm. For Heilbrunn, viscosity *was* structure, especially so if it was hard to observe colloidal particles in living cells. What Heilbrunn wanted to know was how the viscosity of protoplasm changed in relation to both its external environment — temperature, salt concentrations, atmospheric pressure, exposure to solvents — and as the protoplasm of the egg itself went through the normal stages of life. His baseline measurement of sea urchin egg protoplasm (at seven times the viscosity of water) allowed him compare the changing changes in viscosity as, for example, the egg was fertilized (Figure 3.7), or if the egg was wounded, or as the egg was exposed to cytological fixatives.[53] For Heilbrunn, any dramatic change in the viscosity of protoplasm was a sign of a major life event.

For both Heilbrunn and MacDougal, carefully measuring the viscosity of protoplasm or trying to build an artificial cell made sense only within the assumptions and metaphysical expectations of colloid chemistry, especially in its earlier forms. Although both assumed that protoplasm was complex mixture, they also assumed that breaking down and analyzing cells' and protoplasm's constituent parts would destroy the physical properties protoplasm had in its natural state. Heilbrunn conducted his viscosity measurements knowing that he would only be able to find the average viscosity across the whole sea urchin egg. Likewise MacDougal admitted that one of his

52. L. V. Heilbrunn, *The Colloid Chemistry of Protoplasm*, 8.

53. L. V. Heilbrunn, "Protoplasmic Viscosity Changes during Mitosis."

motivations for building artificial cells was their scale: they were easier to work with, and it would be trivial to build new ones with different material arrangements. MacDougal wanted to know how different material systems might behave in a specific biotic environments, and the idea that cells were complex colloids essentially gave him a reasonable justification to try building and testing a (less) complex colloid as an analogy to a living cell.

MacDougal and Heilbrunn were just two examples of a rapidly growing area of research. In 1926 the journal *Protoplasma* began publication, as a self-described "international journal of the physical chemistry of the protoplasm; two years later the series *Protoplasma-Monographien* was inaugurated, with Heilbrunn's *The Colloid Chemistry of the Protoplasm* as its first volume. *Protoplasma* and *Protoplasma-Monographien* became places for biologists to publish biophysical research, often using whatever biological systems they were familiar with — plant or animal, higher or lower organisms. Compared to the standard-bearers of colloid chemistry, the *Kolloid-Zeitschrift* and the *Kolloidchemische Beihefte*, in their early years *Protoplasma* and *Protoplasma-Monographien* were far less technically sophisticated. *Protoplasma-Monographien* became the unfortunately-titled *Protoplasmatologia* in 1954, and changed its name again in 1975 to *Cell Biology Monographs* before ending publication in 1984; the journal *Protoplasma* is still an active general cell biology journal.

On September 29 to October 1, 1930, the Faraday Society at Cambridge organized a major international symposium on "Colloid Science Applied to Biology" — one of the last and largest such symposia in colloid biophysics before the trend towards molecularization began in earnest. The symposium was divided into two parts, one specifically dedicated to protein systems, the other to "the structure of living matter" more generally.[54] The 1930 Faraday Society meeting might be better known today for being one of the earliest public trials of Rudolf Peters' cytoskeleton theory —

54. T. Martin Lowry et al., "Colloid Science Applied to Biology," *Transactions of the Faraday Society* 26 (1930): 663–66.

Peters' paper was almost universally panned. Peters tried to argue that the intensity of biochemical reactions that occur within a cell seemed to be mismatched with the cell's apparent lack of visible structure; from here, Peters argued that a protein "mosaic" could be imagined to isolate enzymes and biochemical reactions in small pockets.[55] Most of the participants agreed with Frederic Donnan that protoplasm was not viscous enough, or that surface phenomena could account for the metabolic discrepancies that were bothering Peters; the mathematician Dorothea Wrinch rather incisively pointed out that Peters had supplied no mathematical justification for his concerns.[56]

With the exception of Peters' poor performance, most of the attendees of the 1930 Faraday Society meeting seemed very optimistic about the future of colloid chemistry in biology. The pair of general commentaries by W. B. Hardy and the biochemist Frederick Gowland Hopkins (1861–1947) presented interesting, and in retrospect unexpected contrasts. Hardy offered that,

> The verbal discussions revealed the welcome fact that physicists, chemists, and biologists understand one another. The curious dichotomy of the eighties and early nineties is now healed…Signs there are in plenty that the next great advance in knowledge is due from the biological side. At the present moment biology is over-charged with facts — indocile creatures which need that "mysterious priest" the mathematical physicist to lead them to the altar…[57]

Hopkins, who by 1930 was the elder statesman of English biochemistry, was far more downbeat about his own discipline.

> If, however, we are to assign this great influence to surface catalysis and surface control, we must admit that the surfaces concerned have properties not possessed by those which separate the phases of ordinary artificial colloidal systems. As I have already confessed such remarks merely emphasise the obvious. But on occasions like this, when the biochemist is under the serene gaze of professors of more exact science, he becomes anxious to remind them of the complexity of his materials, and to point out that every attempt however justifiable to analyse the phenomena they display must keep in touch with the reality which is inherent in that complexity.[58]

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55. Rudolph Peters, "Surface Structure in the Integration of Cell Activity," *Transactions of the Faraday Society* 26 (1930): 797–807.

56. General discussion to Rudolph Albert Peters, "Surface Structure in the Integration of Cell Activity."

57. William B. Hardy, "Conclusion," *Transactions of the Faraday Society* 26 (1930): 864–65.

58. F. Gowland Hopkins, "Introductory Remarks on the Structure of Living Matter," *Transactions of the Faraday Society* 26 (1930): 770–71.

Hopkins was one of the few of the approximately 250 attendees of the meeting to be in support of Peters' protein mosaic theory — hence his discomfort with his colleagues' repeated insistence that surface phenomena could account for most of the cell's biochemical activity. Yet his anxiety that biochemistry had become a domain in possession of too much complexity, and biophysics a domain of careful experimental control, feels counterintuitive in retrospect: most of our historical narratives about post-1930 biochemisty, colloid chemistry, and biophysics emphasizes the intensification and dramatic successes of biochemistry in the subsequent decades.

c. *The historiography of biochemistry and the "Dark Age of Biocolloidology"*

In 1972 a particularly egregious example of Whiggish historiography of science was published: Marcel Florkin's *A History of Biochemistry*, its five volumes a capstone to his thirty-four volume reference work, *Comprehensive Biochemistry.* The whole series was an exercise in boundary setting, meant to define what was proper biochemical science. "The Dark Age of Biocolloidology, 1900–1940" was the title of Florkin's shortest chapter, its five pages consisting mostly of long, untranslated block quotes, exemplifying what he believed was biologists' "overvalorization" of colloidal theory that lasted into the 1940s. Florkin later clarified in a chapter on "The Recognition of the Proteins as Truly Defined Macromolecules," that "The theory of the 'colloidal state' with its overvalorized 'biological' virtues was very popular among biologists."[59] For Florkin this was essentially the period in which biologists believed proteins were colloidal aggregates, clumps of smaller molecules held together in a jelly-like state, the "colloid state" of aggregation. The correct biochemical idea for Florkin was that proteins were proper chemical molecules, held together by secondary valence bonds, as they were understood in analytic and organic chemistry: *i.e.,* chemical

59. Marcel Florkin, *A History of Biochemistry*, Comprehensive Biochemistry, vol. 30 (Amsterdam: Elsevier, 1972) 291.

atoms bonded together in specific arrangements. After Florkin died in 1979, Pierre Laszlo reconstructed a sixth volume from Florkin's notes, reproducing Florkin's thoughts even more succinctly:

> Anti-mechanistic, anti-reductionist schools of thought, such as that of the colloid chemists, have acquired a bad reputation. Colloid chemistry is being blamed, quite generally and with good justification, for the protracted emergence of molecular concepts in biochemistry. Arguments for the irreducibility of biology to physics and chemistry periodically spring up, to be put down rapidly on various grounds, most often that of circularity.[60]

The "Dark Age of Biocolloidology" was not merely a time when a bad theory of matter held sway: it was the last the centuries of vitalistic, anti-reductionistic, and anti-scientific impediments that biochemistry overcame before its post-1940 triumph as a "mechanistic and [a] part of soulless science."[61]

This label, "The Dark Age of Biocolloidology," has stuck, tenaciously, and it continues to be cited approvingly by professional historians of science and amateur historians alike.[62] There have been some historians of science since 1972 who have criticized Florkin's wholesale dismissal of an entire period of history — a period that was arguably the formative period for the modern discipline known as biochemistry.[63] Joseph Fruton in particular has argued that Florkin "oversimplifies and overdramatizes the complex development between 1897 and 1930 of the study of the nature of enzyme action…[dismissing] the importance of the physical-chemical approach to that problem at a

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60. Pierre Laszlo, *Molecular Correlates of Biological Concepts*, Comprehensive Biochemistry vol. 34A (Amsterdam: Elsevier, 1986), 156.

61. Marcel Florkin, *A History of Biochemistry*, 316.

62. Ute Deichmann, "'Molecular' versus 'colloidal': Controversies in Biology and Biochemistry, 1900–1940," *Bulletin for the History of Chemistry* 32 (2007): 105–18; Charles Tanford and Jacqueline A. Reynolds, *Nature's Robots: A History of Proteins* (Oxford: Oxford University Press, 2001), chapter 4; Graeme K. Hunter, *Vital Forces: The Discovery of the Molecular Basis of Life* (San Diego: Academic Press, 2000) 157.

63. Within the history of biochemistry, for example: Robert E. Kohler, "The Background to Otto Warburg's Conception of the 'Atmungsferment,'" *Journal of the History of Biology* 6, no. 2 (October 1, 1973): 171–92; Robert E. Kohler, *From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline* (Cambridge: Cambridge University Press, 1982); William Bechtel, *Discovering Cell Mechanisms: The Creation of Modern Cell Biology* (Cambridge: Cambridge University Press, 2008), 94; James E. Strick, *Wilhelm Reich, Biologist* (Harvard University Press, 2015), 150;.

time when the chemical nature of catalytic agents in enzymatic reactions was in doubt."[64] Yet Florkin's more basic argument has stood: that this period was a struggle of colloids versus macromolecules, and that in this period there was a historical progression "from" colloids "to" protein macromolecules; it has stood even in Andrew Ede's attempt to excavate colloid science in his disciplinary history of the same.[65] In particular, Florkin and most other historians of biochemistry tend to see colloid chemistry *only* as a theory of aggregation, rather than as a larger-scale approach to complex materials. The micellar theory in particular (to be discussed in the next chapter) has come under criticism as an untrue or unproductive theory of particle aggregation. This historical narrative of "colloid vs. macromolecule" persists because the history of biochemistry has long been written as a history of discoveries of particular biochemical pathways, enzymes, and catalysts — a history that usually culminates in the discovery of the DNA double-helix and the Central Dogma of protein synthesis in the 1950s and '60s.[66]

As a result, a great deal of this flawed historical narrative revolves around debates over the maximum size of a molecule. According to this history, which has been studied most closely by the historian of polymer chemistry Yasu Furukawa, from ca. 1910 to the 1940 chemists believed that molecules above a certain size could not exist, and that compounds above this size were held together into "colloids" or "micelles", *i.e.,* large aggregate substances held together by tertiary surface forces, rather than secondary valence forces. In the early 1910s, organic chemists concluded that the largest molecule with "well defined individuality and known structure" had a molecular weight of 4,021 — Emil Fischer's "hepta-(tribenzoyl-galloyl)-p-iodophenol-maltosazone.[67] Before 1913, attempts to

64. Joseph S. Fruton, *Proteins, Enzymes, Genes: The Interplay of Chemistry and Biology* (New Haven: Yale University Press, 1999), 158.

65. Ede's last chapter in *The Rise and Decline of Colloid Science in North America* is "Micelle versus Macromolecule."

66. Ute Deichmann, "Crystals, Colloids, or Molecules? Early Controversies about the Origin of Life and Synthetic Life," *Perspectives in Biology and Medicine* 55, no. 4 (2012): 521–42.

67. Emil Fischer and Karl Freudenberg, "Über das Tannin und die Synthese ähnlicher Stoffe. III. Hochmolekulare

measure the molecular weight of complex proteins like haemoglobin using traditional organic chemical methods had returned molecular weights in the tens of thousands. Fischer, who was one of the most influential organic chemists before WWI, declared that any size measurement above 5,000 was most likely due to poor technique, the persistence of impurities during the purification process needed to make this kind of molecular weight determination. Everything above 5,000 was the result of some other aggregative process, *not* valence bonding in the traditional, Berzelian, organic-chemical sense. In the 1920s, however, the chemist Hermann Staudinger began to argue that larger, "macromolecular" particles existed, with weights not just in the tens of thousands, but conceivably up to the hundreds of thousands, or perhaps even to unlimited dimensions, as he colorfully suggested with his hypothetical chemical formulae using ellipses at either end (Figure 3.8). Staudinger famously fought with colloid chemists (even though his first university position was in colloid chemistry) and organic chemists alike through the 1930s. After a number of twists and turns, Staudinger was finally vindicated in the 1940s, and received the Nobel Prize in 1953 for having discovered and demonstrated the existence of true macromolecules.[68]

This emphasis on Staudinger and the history of macromolecular biochemistry misses a significant and what appears to be a fairly robust area of biological research in the interwar period: the development of theories of biological structure and function based on quantifiable physical phenomena at the scale of whole cells. Biology had come to embrace colloid chemistry as a way of answering long-standing questions about the structure and behaviors of protoplasm, with biologists hoping to bring their science closer in line with physics. These concerns about the nature of living matter were far away from the biochemists' disciplinary concerns about specific chemical reactions

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Verbindungen," *Berichte der deutschen chemischen Gesellschaft* 46, no. 1 (January 1913): 1116–38.

68. Yasu Furukawa, *Inventing Polymer Science: Staudinger, Carothers, and the Emergence of Macromolecular Chemistry* (Philadelphia: University of Pennsylvania Press, 1998); and Yasu Furukawa, "Hermann Staudinger and the Emergence of the Macromolecular Concept," *Historia Scientiarum* 22 (1982): 1–18.

within cells, or any theory of enzyme action, or even issues of metabolism and nutrition. As the next two chapters will show, even as biologists moved on from a colloidal to a molecular ontology, they were still guided by the same questions about the nature and structure of protoplasm — only rather than quantify protoplasm's viscosity or permeability, these early molecular biologists in the 1930s sought to reveal protoplasm's visible structure. As for the larger group of biologists like Heilbrunn working colloid physical chemistry, we cannot yet confidently say where these early biophysicists went or what they did after the Second World War: their presence in historical memory seems to have been obscured by the genuinely revolutionary discoveries in the new biophysics and biochemistry that developed in the 1950s.[69]

69. The reviewer of Andrew Ede's history of colloid science noted that "Ede's inability to deliver the definitive account of the rise and fall of colloid science stems from his narrow view of the book's remit," *i.e.,* the geographical limitation to North America. Peter J. T. Morris, review of *The Rise and Decline of Colloid Science in North America, 1900–1935: The Neglected Dimension*, by Andrew Ede, *Isis* 100, no. 1 (March 2009): 171–72.

Chapter 4: Crystals, Colloids, and Fibers

> The wonderful order of the parts into a whole, which is exemplified by the animal body, extends not only over the visible segments, organs, tissues, cells, intercellular and cuticular substances and their microscopic building blocks, but in the same way also reigns in the submicroscopic domain down to the molecular realm. The present conditions are of great, indeed fundamental importance for morphology and physiology especially. For all of the structures and powers of the higher levels appear as the results of molecular events, and they can ultimately be explained only by causal reference to generally material forces. For the scientist there is no other way to understand the whole than by more deeply penetrating and analyzing the interplay of the parts.
>
> — W. J. Schmidt, " Molekulare Bauweisen tierischer Zellen und Gewebe," 1938[1]

Eight months before he died in April 1927, the German botanist Hermann Ambronn (1856–1927) was fêted in typical German academic fashion: on August 11, 1926, a gathering of friends, admirers, and students in celebration of Ambronn's seventieth birthday. It was an opportunity to showcase the intellectual legacy of a scientist, even though his fame and influence had arrived only ten years prior. Ambronn's single-minded devotion to a mid-nineteenth century botanical concept, the *micelle* or *"Mizelle,"* had made him one of the most celebrated colloid theorists of the 1920s, and his well-timed passing spared him from the later recriminations and repudiations of an idea he had so vigorously defended. The word "micelle" had been coined in 1877 by the famous German botanist Carl Nägeli (1817-1891) to designate the submicroscopic crystalline or semi-crystalline particles that he believed composed a wide variety of plant substances, ranging from starch granules to cell walls. Nägeli's micelle had gained few other adherents beyond a few botanists, and had all but disappeared by the 1890s — so, unsurprisingly, Ambronn was greeted with a great deal of skepticism in 1916 when he declared that micelles were the fundamental fine-structural unit

1. W. J. Schmidt, "Molekulare Bauweisen tierischer Zellen und Gewebe und ihre polarisationsoptische Erforschung," *Naturwissenschaften* 26, no. 30–31 (July–August, 1938): 481–90, 509–14.

of all colloidal gels. Ten years later the micelle was almost universally lauded and accepted as a wide ranging theory of colloidal structure. In the salad days of colloid chemistry, the *Ambronnfest* brought together the kind of diverse collection of disciplines that only a colloidist could appreciate: a synopsis of the festschrift published in *Naturwissenschaften* highlighted the impact of Ambronn's work on botany, mineralogy, animal histology, colloid chemistry, and crucially on scientific (*wissenschaftliche*) microscopy. From his vantage point at the eve of his passing, a wide range of scientists across this wide range of disciplines had come to see the micelle as a crucial theory of material structure. Yet, within a few decades the micelle was dead and forgotten as well, the victim of colloid chemistry's collapsing disciplinary relevance. When he was asked about the micelle in a 1986 interview, the physical chemist Herman Mark (1895–1992) only remarked, "I couldn't care less" — when, in fact, he and his collaborator Kurt Meyer (1883–1952) had been two of the micelle's most important proponents and theorists in the 1920s and '30s.[2]

What made the micelle so important in the 1920s and '30s? This chapter will argue that the micellar theory of colloidal structure, and in particular Ambronn's approach to studying colloids, vigorously reintroduced both microphysical theorizing and visual methods to colloid chemistry. Colloid chemists had been averse to both, but Ambronn introduced a set of material concepts and laboratory techniques that became useful for disaggregating heterogeneous colloids into their separate parts and making those parts available for optical study. Today, micelles are mostly only known in soap chemistry as tiny, monolayer vesicles of fatty lipids; the International Union of Pure and Applied Chemistry's official definition of the micelle is a "particle of colloidal dimensions that exists in equilibrium with the molecules or ions in solution from which it is formed."[3] But, as this

2. Mark, Herman F. Interview by James J. Bohning and Jeffrey L. Sturchio, 3 February, 17 March, and 20 June 1986. Beckman Center for the History of Chemistry Oral History Program.

3. Stanislaw Slomkowski et al., "Terminology of Polymers and Polymerization Processes in Dispersed Systems (IUPAC Recommendations 2011)," *Pure and Applied Chemistry* 83, no. 12 (2011): 2229–59, on 2240, §5.10. See also Brian Vincent, "McBain and the Centenary of the Micelle," *Advances in Colloid and Interface Science* 203 (January 2014): 51–

chapter will show, in biology the micellar theory's importance reached beyond theories of colloidal structure, and it had little to do with ions, soaps, or micelles. In biology the micelle re-legitimized the visual study of fibrous and crystalline parts of the cell and protoplasm that had been cast aside by biologists' attempts to formulate a general, colloidal theory of protoplasm's soft, fluid-like structure. If after 1899 biologists largely gave up on trying to find a visible structure in protoplasm, Ambronn's micellar theory reopened the possibility for a new kind of "submicroscopic morphology" of protoplasm, and a way of explaining life through the exploration of its fine structure.

To a certain extent, both this chapter and the next tell the history of how Ambronn's theories and laboratory methods established submicroscopic morphology as a significant subfield in the life sciences — better known in the American context as either ultrastructure research or cell-structural research. Much of the present chapter is centered around the two biologists whose names were nearly synonymous with micellar theory in the twentieth century: Ambronn and his student Albert Frey-Wyssling's (1900–1988, *née* Frey, before he married Margarit Wyssling in 1928). Although narrative focus on two individuals is a departure from the discourse-scale analysis in the first chapters of this dissertation, both Ambronn and Frey-Wyssling alternated between botany and scientific microscopy during their careers; a close examination of these two individuals reveals much about the intimate connection between their ideas of matter and the techniques in microscopy they developed to make the invisible structure of matter visible. To situate Ambronn's recovery of the micelle, this chapter reaches back into the nineteenth century to examine biologists' initial rejection of Carl Nägeli's micellar theory in the 1880s. This brief and revealing episode not only provides context to Ambronn's early career struggles, but also shows how biologists engaged with late-nineteenth century

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physics became skeptical of discontinuous theories of matter, even before their embrace of colloid chemistry.

As well as being a history of the micelle, this chapter is also a history of polarized light microscopy, the technique to which the micelle was indelibly linked within biology as early as the 1870s; Ambronn devoted his entire career to the technique, and Frey-Wyssling was one of the most important theorists of polarized light microscopy before he adopted the electron microscope in the 1940s. As its name suggests, polarized light microscopy technique relies on the properties of polarized light — light that vibrates only along one plane perpendicular to its direction of travel — to open up the interpretive possibilities of microscopy beyond mere direct observation. But the very nature of polarized light and polarized light microscopy left both the technique and Ambronn alike facing a familiar conundrum: How ought a scientist interpret what could be seen under the microscope? The dazzling colors and interference patterns visible through the polarized light microscope are beautiful, even psychedelic, and Ambronn's friends remembered his fondness of "conjuring up the 'aesthetic dimension of science' on a projection screen."[4] But, given the variety of optical theories and theories of matter, which theory best explained shifting colors and bands of light? Were they caused by properties of the material itself? Some but not all of its parts? Were optical phenomena the result of external physical forces, or the product of an object's own structural properties? The challenge that Ambronn faced in the early twentieth century was the same one that Carl Nägeli had faced late in the nineteenth century: convincing the larger community of biologists and physicists that an indirect optical phenomenon was produced by a fundamentally invisible material structure.

4. Albert Frey-Wyssling, *Albert Frey-Wyssling: Lehre und Forschung: autobiographische Errinerungen*, Grosse Naturforscher, Bd. 44 (Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1984), 50.

Polarized light microscopy is discussed in greater detail in **Appendix A**, which includes some polarized light micrographs, but briefly: polarization microscopy detects *anisotropy*, or generally oriented or directed patterns, most crucially in *birefringent* materials, which have different refractive indices that change with the direction and polarization of light. Polarized light microscopy had been used for centuries in mineralogy as an essential aid in classification and identification of crystals, and since the 1810s polarized light more generally played a significant role in the development of wave theories of light. From its invention in 1828 and up through the 1950s, the best optical device used to polarize light was the Nicol prism, a rhombohedral crystal of Iceland spar with its faces cut at 68°, then cut diagonally in half, and then rejoined with Canada balsam. (Canada balsam was also used in creating permanent microscope specimen slides and in cementing compound lenses, and will play a larger role in Ambronn's story.) In polarized light microscopy, two Nicol prisms are "crossed," positioned so that their planes of polarization are perpendicular to each other: the *polarizer* sits below the condenser, and the *analyzer* is placed between the objective and the eyepiece. Looking through the eyepiece at an empty stage, the observer will only see darkness, since the analyzer has blocked out all of the light let through by the polarizer. However, if a birefringent specimen is placed on the stage — *i.e.*, a specimen that is itself capable of twisting and re-polarizing the vibration of light in some fashion — then the object will appear, illuminated against a dark background, and rendered in a shimmering rainbow of color fringes and interference patterns due to the differing angles and intensities of the specimen's birefringent properties.[5] To the biologists who gathered around Ambronn's laboratory and knew the German slang, the 1920s and '30s became the decades of the

5. More specifically, a birefringent material is one whose refractive index (n) differs depending on both the plane of polarization of light and the direction in which it is traveling. The two extreme values of refractive indices are n_e and n_o (sometimes labeled ε and ω), designating the refractive indices for the *extraordinary ray* (or *e-ray*) and the *ordinary ray* (or *o-ray*). The ordinary ray travels through the crystal obeying the normal laws of refraction, *i.e.* traveling at the same velocity in every direction of the crystal. The extraordinary ray does not obey the normal laws of refraction: its velocity depends on the direction it is traveling and the plane of polarization.

"crossed Nicols," as much, if not more, than they were the decades of the micelle. With the use of additional filters or "compensators" inserted between the analyzer and the eyepiece, the observer can determine whether the specimen is *negatively birefringent* or *positively birefringent*; this *sign of birefringence* is often used to classify minerals and crystals.[6]

There are significant advantages to examining the history of the micellar theory through the history of polarized light microscopy, rather than simply focusing on the eventual failure of the micellar theory as part of the broader rejection of colloid chemistry. Because the historiography of interwar physical chemistry has long fixated on the opposition and conflicts between colloid and structural-organic chemistry, historians have preferred to focus on the micelle only insofar as it was a part of the decline of colloid chemistry around the Second World War. The micelle, in this historiography, was a holdout belief that small molecules, limited to a maximum size, were held together into colloidal aggregates by a "tertiary," inter-molecular force — e.g., a micellar force or, today, the so-called van der Waals force.[7] The issues around molecular weights were genuine, but focusing on the triumph of the more "reductionistic" polymer chemists against holistic, colloidal "aggregationists" places the historical emphasis on a limited number of disciplines and problem areas, namely organic chemistry and biochemistry, which had largely been concerned with stoichiometric reactions, metabolic processes, and enzymology. In addition, focusing on a narrative of "colloid

6. In a negatively birefringent material, the ordinary ray travels more slowly than the extraordinary ray; rendered in terms of the refractive indices of the material, $n_e < n_o$. In a positively birefringent material, the ordinary ray travels faster than the extraordinary ray, so $n_e > n_o$. (Remember that n designates refractive index, so the higher value of n, the slower the light is traveling.) More advanced, variable compensators can assist in quantitatively determining the strength of birefringence in a material, giving a numerical value for $|n_e - n_o|$.

7. The theme of "micelle vs. macromolecule" is another way of opposing colloidal and polymer/macromolecular chemistry, and is very present in Yasu Furukawa, *Inventing Polymer Science: Staudinger, Carothers, and the Emergence of Macromolecular Chemistry* (Philadelphia: University of Pennsylvania Press, 1998); Yasu Furukawa, "Hermann Staudinger and the Emergence of the Macromolecular Concept," *Historia Scientiarum* 22 (1982): 1–18; and Andrew Ede, *The Rise and Decline of Colloid Science in North America, 1900-1935: The Neglected Dimension* (Burlington: Ashgate, 2007). In fact, Ede's last chapter is titled "Micelle versus Macromolecule." For a very internalist history of the van der Waals force, see J.S. Rowlinson, *Cohesion: A Scientific History of Intermolecular Forces* (Cambridge University Press, 2005), 183–210.

versus macromolecule" or "micelle versus macromolecule" ignores the fact that colloidal, micellar, and macromolecular theories were not historically considered incommensurable until later in the twentieth century, and they were often thought of as complementary within the larger scope of physical chemistry.

The micellar theory developed out of a broader interest in the physical structure and the optical behavior of biological matter, *i.e.* protoplasm. The methodological and epistemological concerns around issues of cellular structure and behavior were of interest to both a significant number and variety of biologists; histories that focus only on why the micelle was eventually discredited run the risk of missing why the micelle came out of the hinterlands of botany, and how it so quickly entered into theories of biological material- and fine-structure, as well as into colloid chemical theory more generally. Focusing solely on the ultimate units of matter (*e.g.,* "micelle versus macromolecule") cannot help us address how scientists thought organization could arise out from smaller or larger units.[8] Instead, this chapter will focus on how arguments about the proper role of microscopy and visual analysis affected how biologists thought about about the material-structural parts of larger, biological wholes. In order to avoid the over-simplified histories of "micelle versus macromolecule" or "molecular versus colloidal," this chapter necessarily contains a convergence of the major themes running through this dissertation: the structure and nature of living matter, the epistemology of microscopy, the continuity/discontinuity of matter, and the legitimacy of visual and imaginative reasoning in colloid chemistry and other physical sciences.

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8. cf. Robert C. Olby, *The Path to the Double Helix* (Seattle: University of Washington Press, 1974), chapters 1 and 3; Angela N. H. Creager, "Producing Molecular Therapeutics from Human Blood: Edwin Cohn's Wartime Enterprise," in *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*, ed. Soraya de Chadarevian and Harmke Kamminga (Amsterdam: Harwood Academic, 1998), 107–38, especially on 112; Robert C. Olby, "The Significance of the Macromolecules in the Historiography of Molecular Biology," *History and Philosophy of the Life Sciences* 1, no. 2 (1979): 185–98; and Ute Deichmann, "'Molecular' versus 'colloidal': Controversies in Biology and Biochemistry, 1900–1940," *Bulletin for the History of Chemistry* 32 (2007): 105–18.

This chapter will proceed in four parts, following the long history of the micelle and the polarized light studies of colloidal materials. First is an overview of the early history of the micellar theory: its origin as a botanically-informed theory of structure, Nägeli's work to connect micelles to polarized light microscopy, and the critiques of the micellar theory by microscopists that drove the theory underground for three decades. The second and third parts will look at Hermann Ambronn's recovery of micellar theory, in part two within botany, in part three within colloid chemistry. The third section in particular will situate this recovery within Ambronn's biography as he became both a research technologist and an important manager at the Carl Zeiss optical works.[9] Within the institutional and intellectual setting at the Zeiss Werke, Ambronn and his colleagues combined new microscopic techniques with the new technique of x-ray crystallography to synthesize colloid chemical theory with Nägeli's old micellar theory. The fourth section will show how Ambronn's student, Frey-Wyssling, developed a "principle of repetition" within micellar theory, and how the micellar theory evolved in his hands into a molecular theory of fiber structure. Finally, the conclusion of this chapter will make some speculations about the post-WWII displacement of micellar theory and micellar diagrams by electron micrographs.

a. Nägeli's "molecules" and the micelle

The first time the word "micelle" appeared in print, the term was nearly an afterthought. It first appeared in 1877, in a footnote in the second edition of Carl Nägeli and Simon Schwendener's (1829–1919) famous microscopy manual *Das Mikroskop*, where it was explained parenthetically as "molecular groups" ("*Molecülgruppen*"), as if the latter term had a single, obvious meaning.[10]

9. On the research-technology matrix, see Terry Shinn, "Research-Technology Instrumentation: The Place of Chemistry," in *From Classical to Modern Chemistry: The Instrumental Revolution*, ed. Peter J. T. Morris (Royal Society of Chemistry, 2002), 95–110.

Apparently Nägeli and Schwendener expected that German botanists well trained in their classical languages would immediately recognize that it was a reference to the Latin term "*micellum*," the diminutive form of "mica" or "crumb." Two years later Nägeli admitted that he had a habit of coining terms and then not explaining them, causing his colleagues to suffer from some "etymological irritations," especially after Wilhelm Pfeffer (1845–1920) began to complain that "micelle" was so similar to the word "cell" that chemists would become confused. Pfeffer had a point: Nägeli was already using the words "atom" and "molecule" in ways that had chemists complaining. Pfeffer's own preferred neologism, "*tagma,*" was Greek for "something arranged."[11] Nägeli responded that, even with the German penchant for mashing together phrases into single words, putting together "mi" with "cellula" would be a "barbaric composition," and that obviously he intended "micelle" to have this more elegant, classical association.[12]

As amusing as this petty quarrel between Nägeli and Pfeffer might be, the larger problem they faced was the conceptual squishiness of the word "molecule" in the 1870s, especially the lack of agreement between chemical and physical conceptions of the term. Nägeli and Pfeffer developed the micelle and tagma explicitly to clarify what the word "molecule" meant within plant physiology, at an historical moment when it was not clear how chemical and physical conceptions of the molecule could come together. This was not simply a matter of importing tools and ideas from other disciplines: their aim was to explain the physiological phenomena found in living plants, not simply to validate chemical or physical concepts. Nägeli had been using the word "atom" to refer to a smallest, individual particle of any given material, such as starch, whereas the chemists' atom was a smallest, individual unit of a fundamental element; for example, in 1858 Nägeli wrote, "the starch

10. Carl Nägeli and Simon Schwendener, *Das Mikroskop: Theorie und Anwendung Desselben*, 2nd ed. (Leipzig: W. Engelmann, 1877), 323.
11. Wilhelm Pfeffer, *Osmotische Untersuchungen: Studien Zur Zellmechanik*, (Leipzig: W. Engelmann, 1877), 32, 150ff.
12. Carl Nägeli, *Theorie der Gärung: ein Beitrag zur Molekularphysiologie* (Munich: R. Oldenbourg, 1879), 121.

atom is composed of 12 atoms of carbon, 10 atoms of hydrogen, and 10 atoms of oxygen."[13] Likewise, between 1858 and 1877 Nägeli used the word "molecule" to refer to aggregates of atoms bound together by chemical forces — but unlike the chemists' concept of molecular species, Nägeli put no upper or lower limit to how many atoms were bound together in any given molecule.[14] And for all of Nägeli's use of the terms "atom" and "molecule," he also seemed unaware that, in the eyes of physicists, these terms might commit him to a position on the atomicity and fundamental discontinuity of matter.

For Nägeli, whole point of using the terms "atom," "molecule," and eventually "micelle" was not to proclaim a new metaphysics, but rather to explain phenomena like the swelling of cell walls or of microscopic starch granules. The theory relied on an analogue to Newtonian mechanics on the one hand, and organic-chemical analysis on the other. In his monograph on starch granules, Nägeli argued that the swelling, drying, and cracking of starch granules could be explained by the intussusception of watery layers or a fluid atmosphere ("*eine Flüssigkeitsatmosphäre*") between the molecules — without also suggesting that the water itself might have a molecular constitution (Figure 4.1).[15] Nägeli went much further than simply arguing by analogy: he argued that he could show that the thickness of the layer of water imposed between two starch "molecules" was in inverse proportion to the size of those same starch molecules, making his intermolecular force look similar to the inverse square law of gravity.[16] His attempt at demonstrating a new fundamental force — one that worked by action at a distance, also analogous to gravity — culminated in three tables comparing the diameters of starch molecules, the distances between two identically-sized starch

13. Carl Nägeli, *Die Stärkekörner: Morphologische, physiologische, chemisch-physicalische und systematisch-botanische Monographie* (Zürich: Friedrich Schulthess, 1858), 332.

14. *ibid.,* 333; see also J. S. Wilkie, "Nägeli's Work on the Fine Structure of Living Matter," *Annals of Science* 16–17 (1960–61): 11–42, 171–207, 209–38, 27–62, on 19–20.

15. Carl Nägeli, *Die Stärkekörner* 342; see also J. S. Wilkie, "Nägeli's Work on the Fine Structure of Living Matter," 60.

16. J. S. Wilkie, "Nägeli's Work on the Fine Structure of Living Matter," 23–26.

molecules, and the ratio of water to starch; the tables considered cases each of cubic, dodecahedral, and spherical molecules (Figure 4.2).[17]

For the next two decades Nägeli sought other physicalist frameworks to buttress his molecular/micellar theory — though, problematically, he never abandoned his initial Newtonian approach. Through the 1860s, as he and Schwendener were working on the first edition of *Das Mikroskop*, Nägeli worked to incorporate polarization-optical evidence into his molecular theory. Nägeli's move to tie light birefringence and ether physics to his molecular hypothesis lent his theory both wider attention and sharper criticism. Before 1860, a few German biologists were beginning to explore polarized light studies to create additional criteria for classifying organisms and organic substances — but no other biologist was using polarized light microscopy to try to move into speculative physics. For example, Karl von Erlach, working in 1847, was concerned only with adding descriptions of birefringence phenomena to his classification of organic substances. Christian Gottfried Ehrenberg in 1849 had gone slightly further, using polarization microscopy to find out which anatomical structures were genuine crystals (and thus "organized" substances) that showed birefringence, and which anatomical objects showed birefringence only when placed under mechanical strain*, e.g.* pulling or compressing the object. In 1858 Hugo von Mohl sought to push polarization optical analysis further by borrowing from chemical and mineralogical practice, identifying chemical species in biological materials by the sign of birefringence (positive or negative) under more careful observation.[18] (Though von Mohl never mentioned Louis Pasteur, a similar

17. Carl Nägeli, *Die Stärkekörner* 351–2.

18. Hugo von Mohl conducted a review of uses of polarized light in botany in 1858, as a prelude to elaborating his own approach: "Die Untersuchung des Pflanzengewebes mit Hülfe des polarisirten Lichtes," *Botanische Zeitung* 16, no. 1–2 (January 1858): 1–18.

association of chemical species with the sign of birefringence had led Pasteur to his theory of left- and right-handed crystals in the early 1850s.[19])

In 1862 Nägeli presented five papers at the Royal Bavarian Academy of Sciences, articulating his better-developed theory of molecular structure and birefringence in organic matter.[20] His argument that birefringence phenomena were caused by regular molecular structures relied on an argumentative strategy that would have been familiar to mineralogists and chemists: *i.e.,* that regular interference patterns (light and dark bands, color fringes) were due to regular structures and patterns found in crystals crystals. Biologists, however, had resisted thinking about organic structure as being *actually* crystalline, preferring to think of "organized" organic substances as only analogously crystal-like: minerals with regular structure were pure, and biological structures were not only heterogeneous in composition, they usually formed irregular structures.[21] In order to link polarization-optical phenomena to his molecular hypothesis, Nägeli invented an entirely new class of materials, *crystalloids*, to bridge the ontological gap between crystalline organization and organic organization. Proper crystals were understood to grow by apposition — growth by depositing units around the outside of the crystal in successive layers. Nägeli defined crystalloids as substances that would only appear like crystals in their dry state, but when hydrated, grew by intussusception, the deposition or infiltration of water and new material in the interstices of the micelles, *i.e.* the molecular aggregates.[22]

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19. Seymour H. Mauskopf, "Crystals and Compounds: Molecular Structure and Composition in Nineteenth-Century French Science," *Transactions of the American Philosophical Society* 66, no. 3 (1976): 1–82.

20. These were collected as nos. 5–9 in Carl Nägeli, *Botanische Mittheilungen*, vol. 1 (Münich: F. Straub, 1863); see note 22, below.

21. Russell Maulitz has argued that a "crystallographical mode of explanation" was popular in the nineteenth century, but he stresses that the comparison between organic growth and crystalline growth was always made by analogy, and that biologists like Schwann were at pains to stress the differences. Russell C. Maulitz, "Schwann's Way: Cells and Crystals," *Journal of the History of Medicine and Allied Sciences* 26, no. 4 (1971): 422–37.

22. Carl Nägeli, "Über die crystallähnlichen Proteinkörper und ihre Verschiedenheit von wahren Crystallen," *Sitzungsberichte der königlichen bayerischen Akademie der Wissenschaften* 2 (July 11, 1862): 120–54.

As was the case in his description of starch granules in 1858, this new theory of crystalloid structure allowed Nägeli to define organic matter as composed of tiny individual crystals, the micelles, separated by water or other materials (Figure 4.3), rather than as a single, monolithic crystal. Given this clear ontological difference between inorganic crystals and organic crystalloids, Nägeli argued that the birefringence phenomena in organic materials were necessarily different from those in inorganic ones. Birefringence in a material like glass or calcite would reflect something essential about the *whole* piece of glass or calcite, while birefringence in plant fibers or starch granules would reflect only the properties of the individual molecular/micellar parts. This distinction, between on the one hand the optical behavior of whole, inorganic objects, and on the other hand the optical behavior of the parts that make up up organic objects, was the locus of the debate about the existence of micelles up until Ambronn's resolution of the problem in 1916–17.

The most important optical prediction of Nägeli's micellar theory was that in organized, crystalloid substances, pushing and pulling a specimen would change its optical appearance only if the individual, birefringent micelles moved and realigned. While it was well known that applying mechanical pressure or stress on glass or many other inorganic materials could change its optical properties, Nägeli suggested that a plant fiber or a hair was resistant to such changes, because it was the unique micellar parts that caused birefringence, not the whole fiber or hair.

> Organised substances act in all essential points differently from non-organised ones; their optical character is not, as in the latter, dependent on changes of distance which the smallest particles undergo by pressure or tension, or even by swelling; it remains constant, even when the changes amount to a multiple of the original distances. We can stretch or bend a hair, a bast-fibre, &c. at will, without altering the character of its colours; whilst, for example, a fine glass tube, even on very slight curvature, produces the color which corresponds to the change of distance of atoms thereby occasioned.[23]

Nägeli then described an imaginary model, essentially the same as the one he developed in 1858, but now layered with language about the optical properties of the starch (or other) molecules and the

23. Carl Nägeli and Simon Schwendener, *The Microscope in Theory and Practice*, trans. Frank Crisp and John Mayall Jr. (London: Swan Sonnenschein, Lowrey & co., 1887), 366.

"fluid atmosphere" separating them. "We could artificially recreate a [plant] membrane if we could unite together innumerable small crystals with their [optical] axes oriented in the same way, by using isotropic, elastic ligaments, or with isotropic joints. Such a membrane," Nägeli elaborated, "could be bent, drawn out and pressed together *without changing the interference colors*," because the interference colors were caused by the small parts, and not the membrane as a whole.[24] The anisotropic, optically active micelles in this imaginary model were the substantial portion of the membrane, and they were joined together by the isotropic, *i.e.* optically inactive (and microscopically irrelevant) "joints."

Nägeli's and Schwendener's arguments about the effects of stress on organic substances proved to be the micellar theory's undoing. Although Nägeli and Schwendener had done much to promote polarized light microscopy as a tool to study biological structure, the same tool was now used to oppose Nägeli's micellar theory on several fronts. In 1882 the Bonn botanist Eduard Strasburger (1844–1912) and the Graz animal anatomist Victor von Ebner (1842–1925) directly criticized Nägeli's micellar theory on the grounds that its conceptual elegance hid its fundamental factual deficiencies: Nägeli had relied on his examination of starch granules and cell walls in only a handful of plant species to create his theory. Strasburger and von Ebner undertook far more comprehensive studies than Nägeli had: Strasburger studied the cell walls of a large range of plant taxa and cell types, while von Ebner conducted the first extensive study of vertebrate tissue types under polarized light.

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24. Carl Nägeli, "Beobachtungen über das Verhalten des polarisirten Lichtes gegen pflanzliche Organisation," *Sitzungsberichte der königlichen bayerischen Akademie der Wissenschaften* 1 (March 8, 1862): 290–324, on 311, emphasis added. The original reads: "Wir könnten eine Membran künstlich nachbilden, wenn es gelänge, unendlich viele kleine Crystalle mit gleichlaufender Axenstellung durch elastische aus einer isotrop bleibenden Substanz bestehende Bänder oder Charniere zu vereinigen. Eine solche Membran, könnte man biegen, auseinander ziehen und zusammen drücken, ohne ihre Interferenzfarbe zu ändern."

Strasburger's study was primarily concerned with the growth and structure of cell walls, which he insisted did not grow by intussusception, as Nägeli had argued. Rather, Strasburger believed that cell walls, as well as starch granules, grew by apposition, just like non-organic crystals, and Strasburger claimed to observe starch granules and cell walls alike growing through the depositing of successive layers. In cell walls, this meant the depositing of new material from the inside of the cell by the protoplasm; and in order for such cells to grow in size, the protoplasm would have to push the boundary of its cell outward.[25] Strasburger argued that, if this kind of stress were simply relieved, then the birefringence of a plant cell membrane would completely disappear, contrary to Nägeli's insistence that such stress (or stress relief) would have no optical effect. Moreover, Strasburger argued, if Nägeli's micelles were inherently birefringent, then smashing the starch granule and soaking the powder in water should preserve their birefringent effects — effects that Strasburger said he could not find under crossed polarizers.

Von Ebner's critique was more pointed and more devastating than Strasburger's, and not only because von Ebner was the first animal anatomist to approach Nägeli's micellar theory. Von Ebner directly addressed the more recent physical studies of stress and polarized light, making use of Franz Neumann's equations (ca. 1832) for birefringence in compressed, stretched, unevenly heated, or otherwise stressed glass.[26] Although von Ebner had his suspicions about whether Neumann's law of birefringence could apply to organic materials, he did not share Nägeli's division between inorganic crystalline materials and organic crystalloid ones. Instead, von Ebner found that glass' optical behavior when stressed was identical to that of organic resins, including tragacanth and animal-derived glue. He demonstrated the equivalence by quantifying and correlating the degree of

25. Eduard Strasburger, *Ueber den Bau und das Wachsthum der Zellhäute* (Jena: Gustav Fischer, 1882), 217.

26. See John G. Burke, "Neumann, Franz Ernst," in *Complete Dictionary of Scientific Biography*, vol. 10 (Detroit: Charles Scribner's Sons, 2008), 26–29.

birefringence in glass and resins to the amount of pressure applied, using Neumann's mathematical formulas.[27] Like Strasburger, von Ebner concluded that a large number of birefringence phenomena in animal tissues could be adequately accounted for by assuming that they were under stress, and not because of a sub-microscopic arrangement of invisible, crystalloid, birefringent, micellar particles. In other words, the material might be naturally isotropic, but it was stress, compression or stretch, that caused the material to become *optically* anisotropic: the visible evidence of directionality was not inherent in the material, but was rather caused by some force applied, external to the material itself.

Von Ebner's argument about the effects of stress, as well as the mathematical relationship he plotted between stress and interference colors, essentially black-boxed the question of whether an invisible material structure like Nägeli's micelles could cause visible effects. By asserting that stresses were enough to explain the birefringence visible inside cells, von Ebner did not completely dismiss the possibility that Nägeli might be right in special cases. Yet this small concession by von Ebner also reinforced his larger point: Nägeli may have really seen micelles under polarized light in a very select number of cases, but micelles were not a universal principle of biological structure, let alone the only theory that could explain birefringence effects in living matter. "I believe that the above has been sufficient to show that the hypothesis of the crystalline nature of micelles is highly unlikely," von Ebner wrote. "However, it must also be emphasized that this hypothesis is rather barren as well, that it gives us no deeper insight into the molecular structure of organized substances; on the contrary, for the explanation of many individual cases, special hypotheses which are not connected to the main hypothesis must be called in to help."[28] While von Ebner did not believe he had found enough evidence to say that Nägeli was *entirely* wrong about micelles, von Ebner also displayed a skepticism

27. Victor von Ebner, *Untersuchungen über die Ursachen der Anisotropie organisirter Substanzen* (Leipzig: Wilhelm Engelmann, 1882).

28. *ibid.,* 15–16.

towards microphysical reasoning similar to that of his colleague at the University of Graz, Ernst Mach (1838–1916) — whose experiments on the birefringence of glass and metaphosphoric acid von Ebner cited extensively, and whose exhortation towards positivism and economy in scientific hypotheses had made him infamous as a popular philosopher of science.[29]

Thus, von Ebner made a case that physicists' skepticism towards microphysical reasoning ought to be mimicked in biology as well. From von Ebner's point of view, Nägeli's speculative, Newtonian, mechanical reasoning had no place in physicalist biology in the late nineteenth century, because the epistemologies and explanatory strategies of physicists had decidedly shifted away from that older model. Nägeli's micellar theory by the 1880s was thus not only old fashioned because of its shortage of empirical evidence: it was simply an old fashioned way to do biophysics.

b. Hermann Ambronn in the micellar wilderness

Hermann Ambronn apparently thought of himself as a "loner" — *"ein Einsamer"* — but neither his ideas nor his idealism about micelles and the micellar theory were born in a vacuum.[30] His consistent commitment to thinking in terms of invisible parts and particles came from his longstanding friendship with his mentor Simon Schwendener, Nägeli's assistant, collaborator, and defender of the micellar theory; in the 1890s Ambronn was one of the few botanists who defended Scwhendener against von Ebner's stress hypothesis. The diverse and colorful array of botanists and physicists whose paths Ambronn crossed suggests that, whatever personality traits he gave himself, he

29. See Michael Stöltzner, "Vienna Indeterminism: Mach, Boltzmann, Exner," *Synthese* 119, no. 1/2 (1999): 85–111; David Lindley, *Boltzmann's Atom: The Great Debate That Launched a Revolution in Physics* (New York: Free Press, 2001), chapter 7; and Deborah R. Coen, *Vienna in the Age of Uncertainty: Science, Liberalism, and Private Life* (Chicago: University of Chicago Press, 2007).

30. Both Albert Frey-Wyssling and the geneticist Otto Renner wrote about this self-reflection by Ambronn, though both only knew him towards the end of his career. Otto Renner, "150 Jahre botanische Anstalt zu Jena," *Jenaische Zeitschrift für Medizin und Naturwissenschaft* 78, no. 2 (1947): 131–62; Albert Frey, "Hermann Ambronn," *Berichte der deutschen botanischen Gesellschaft* 45, no. 11 (April 1927): 60–71.

was eventually able to build a recognizable niche as an expert in scientific microscopy and optical theory in the broader German scientific community. A colleague later wrote that Ambronn's ideas "for a long time went nowhere, not because he understood too little, but because the others among his discipline (*Besonderheit*) understood too little. It was not due to their ill will, but rather their incapacity."[31] Considering the sheer talent among plant physiologists of Ambronn's generation and their intense engagement with physics and chemistry, incapacity alone seems an unlikely reason for why Ambronn or his ideas spent so much time in the wilderness. So how was it that Ambronn was intellectually marginalized for so long, and how was it that Ambronn finally convinced his colleagues to believe in the existence of micelles?

Ambronn was not short of important supporters and mentors as a student, and he carried an impressive academic pedigree. In the late 1870s he studied with the botanist Julius Wiesner (1838–1916) in Vienna, and the botanist Leopold Kny (1841–1916) at the University of Berlin, the latter of whom was an expert in both cryptogamic botany and in experimental plant physiology, and had been a student of both Carl Nägeli and Ferdinand Cohn. Ambronn left Vienna to join Kny's plant physiological institute in 1878–80 to work on his doctoral research in 1880 on the morphology of the *Florideaen* red algae.[32] While doing this relatively old-fashioned comparative morphological work, Ambronn fell under the influence of the recently-arrived Schwendener. Schwendener had been recruited to Berlin in 1878 to establish another botanical institute, separate from Kny's institute.[33] By now, Schwendener was not only the co-author of a very important microscopy manual, but he also had a reputation as an advocate of a "physico-mathematical" style of anatomy, focused on studying

31. Otto Renner, "150 Jahre botanische Anstalt zu Jena," 159.

32. Albert Frey, "Hermann Ambronn," *Berichte der deutschen botanischen Gesellschaft,* 61. Frey-Wyssling is unspecific about when Ambronn moved from Vienna to Berlin.

33. Max Lenz, *Geschichte der Königlichen Friedrich-Wilhelms-universität zu Berlin*, vol. 3 (Halle a.d.S.: Buchhandlung des Waisenhauses, 1910), 389–96.

the developmental mechanics of higher plants. Schwendener's approach to plant physiology was similar to Nägeli's, conducted in the spirit of Newtonian mechanics and deploying geometric reasoning to plant structure and growth; Kny's style of experimental intervention would have been more typical in contemporary plant physiology.[34] In the relatively short, two year period that they were in the same city, Schwendener likely introduced Ambronn to polarization microscopy and to Nägeli's micellar theory as well.

After completing his dissertation in 1880, Ambronn moved to Leipzig, where he spent the next nineteen years moving from one temporary, if prestigious, assistantship to another. This transitory existence probably enforced Ambronn's own sense of being a loner in his discipline, but it also exposed him to a broad cross-section of the German physical and biological sciences, and at at a rarified, elite level. In 1881 he became the laboratory assistant to August Schenk (1815–1891) in Leipzig, as well as the curator of the Leipzig herbarium.[35] In 1888 Wilhelm Pfeffer was chosen as Schenk's successor. Pfeffer had become very famous for his precise experimental work on plant cell osmosis, and his collaboration with the Dutch physical chemist Jacobus van't Hoff on chemical kinetics and the gas law.[36] Pfeffer's elevation was likely a blow to Ambronn, whose six years as Schenk's assistant would ordinarily have allowed him to be his successor. Instead, Ambronn retained his assistantship for what must have been an uncomfortable year, now working under a far more famous plant physiologist only ten years his elder. At some point in the 1880s Ambronn returned to and became absorbed by Nägeli and Schwendener's *Das Mikroskop*, by now in its second edition.

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34. Eugene Cittadino, *Nature as the Laboratory: Darwinian Plant Ecology in the German Empire, 1880-1900* (Cambridge: Cambridge University Press, 1990), chapter 4.

35. Albert Frey, "Hermann Ambronn," *Berichte der deutschen botanischen Gesellschaft*, 62.

36. *ibid.,* 61–62. For more on Pfeffer's osmotic work and the van't Hoff's law of solutions, see John W. Servos, *Physical Chemistry from Ostwald to Pauling: The Making of a Science in America* (Princeton: Princeton University Press, 1990), 32; and Diana Kormos Barkan, *Walther Nernst and the Transition to Modern Physical Science* (Cambridge: Cambridge University Press, 1999), 49.

However, his continued support of Schwendener in the latter's various disputes cost him his relationship with Pfeffer. Ambronn later in life recalled an incident in which Pfeffer told Ambronn that his interest in micellar theory was "botanical monkey-business that will do no good" ("*daß seien botanische Allotria, die keinen Nutzen brächten*").[37] Whether out of conviction or obstinacy, Ambronn ignored Pfeffer's advice, bearing enough of a grudge against him to remember the story over thirty years later.

Even in his earliest polarization microscopy work, Ambronn was particularly attentive to the way parts of more obviously heterogeneous materials might interact with one another to create different birefringent effects. His first foray into polarized light microscopy in February 1888 was a paper on cells and plant fibers stained with iodine and eosin.[38] His insight here was to use polarization microscopy to explore the nature of cytological stains, hoping to shed light on both th material nature of the stain and how it interacted with the material substance of the plant cell or fiber. When stained, specimens showed different kinds of *pleochroism* or *dichroism* — that is to say, a specimen would have a different color depending on the angle at which polarized light reflected off of it — not present before they were stained. Ambronn suggested no fewer than six different ways to explain what would come to be known as "dichroic staining." Each of his six hypothetical explanations was based on unproven assumptions about the invisible structure of the cell wall and the nature of the dye, as well as how they interacted. The membrane could either have its own, inherent optical properties, or it could acquire strong optical properties by means of the dye; the dye itself could be a pure solution that penetrated the membrane, or it could be a suspension of particles

37. This remark is quoted in Albert Frey's introductory remarks in *Die Micellartheorie von Carl Nägeli*, ed. Albert Frey, Ostwald's Klassiker der exakten Wissenschaften nr. 227 (Leipzig: Akademische Verlagsgesellschaft M.B.H, 1928), 10.

38. Hermann Ambronn, "Pleochroismus gefärbter Zellmembranen," *Berichte der deutschen botanischen Gesellschaft* 6, no. 2 (March 1888): 85–94.

that surrounded elements (the micelles?) of the membrane. In the latter case, the dye particles could be isotropic or anisotropic.[39]

Ambronn's readiness to hypothesize about the minute details of structures he had not yet seen stood in contrast to von Ebner's general unwillingness to endorse one view or another. On a fundamental, epistemological level, von Ebner was arguing that physical forces acting on matter caused optical phenomena. Ambronn, the old-fashioned adherent to Nägeli's micellar theory, argued that it was the structure of matter itself that caused optical phenomena, and that external forces merely changed an object's material structure. For von Ebner, matter was a black box, the structure of matter was invisible and otherwise inaccessible, but mechanical forces could be measured and quantified; for Ambronn, proving a theory of material structure was more important than correlating a mechanical force with an optical effect. Yet if Ambronn's goal was to tease apart the optical effects of the whole in order to locate their causes at a lower level of organization, then empirically, Ambronn was taking a leap of faith. In an 1889 essay, Ambronn asked of his readers:

> Let us imagine [*Denken wir uns nun*] the micellae as rodlet [*stäbchenförmige*] structures, and assume that, in the particular cases of cherry- and tragacanth resin, the effective optical elasticity ellipse (in the sense given by Nägeli and Schwendener) is oriented with its long axis perpendicular to the longitudinal axis of the rodlet. One can thus easily imagine [*so kann man sich leicht vorstellen*] how, if such a substance is in a swollen state, the effects of stress can cause the micelles to easily and mutually move around, thus an orientation thereof in the same direction can come about, and through all of the parts an overall optical effect would be achieved.[40]

Ambronn was explicitly trying to recreate and re-explain von Ebner's experiments with organic glues and resins, and hoping to use von Ebner's own exemplary materials to demonstrate the validity of micellar theory. Specifically, Ambronn argued that the micellar hypothesis could account for an

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39. *ibid.,* 87–88.

40. Hermann Ambronn, "Das optische Verhalten und die Structur des Kirschgummis," *Berichte der deutschen botanischen Gesellschaft* 7, no. 2 (March 1889): 103–14. The "effective optical elasticity ellipse" Ambronn refers to is a two-dimensional cross section of the three dimensional optical elasticity ellipse (itself a three-dimensional mathematical description of the density or elasticity of the ether). This two-dimensional, "effective" index ellipsoid was a geometrical innovation that allowed Nägeli and Schwendener to reconstruct a three-dimensional index ellipsoid with thin sections of any given material, and with a microscope stage that rotated only in one direction — a necessary practice in the kind of microscopy they were pursuing. See Carl Nägeli and Simon Schwendener, *Das Mikroskop* (1867), 303–29.

"anomalous" optical effect that von Ebner's stress theory could not: immediately after the resin was *released* from pressure, its birefringence briefly intensified, before becoming isotropic again. Rather than systematically rejecting different theories for the causes of birefringence, as von Ebner had done in 1882, Ambronn here in 1889 looked for cases where von Ebner's stress theory could not account for all birefringence phenomena. With cherry resin, Ambronn wanted to claim that stress and micellar orientation worked in tandem. Trying open von Ebner's black box, Ambronn imagined that birefringent micelles could move and realign in their medium as a response to stress.

The only elements in Ambronn's micellar theory were the micelles, conceived as birefringent, rod-like structures that were capable of moving around in unison when the larger material was mechanically stressed. Ambronn was not trying to preserve all of Nägeli's speculative Newtonian analogies, nor Nägeli's classification of crystalloid materials, nor any of Nägeli's physiological theories of fermentation or metabolism; neither did Ambronn not care to maintain Nägeli's insistence that organic and inorganic matter grew differently, or Nägeli's clumsy attempts to align his theory with Kekulé's theories of molecular aggregation. In the 1920s, this essay on the optical behavior of tree resins would be recognized as a major, early defense of Nägeli's theory — but in 1889 it was still a highly speculative piece, and by itself it was not convincing enough to resurrect the micelle.

For Ambronn personally, the 1889 article was merely a prelude to a decade of intense theoretical work in polarized light microscopy; he did not substantively invoke or discuss micelles again until 1915. The theory continued to play a role in Ambronn's experimental and argumentative strategies, but micelles became more of a mental aid than a material theory that Ambronn tried to prove.[41] In 1889, Ambronn left Pfeffer's laboratory but remained in Leipzig, gaining an appointment as an *Extraordinarius* in medical and pharmaceutical botany, with an additional specialty in the

41. Albert Frey, "Hermann Ambronn," *Berichte der deutschen botanischen Gesellschaft*, 62.

theory and use of microscopes. However, most of the courses he taught were in the theory of microscopy or the use of polarized light for investigation of plant and animal tissues, suggesting that he ignored pharmaceutical botany entirely.[42] His work in the 1890s came out of this strong pedagogical bent: in 1892 he wrote and published a short teaching manual on polarization microscopy, and in 1893 he translated Lazarus Fletcher's short handbook on the geometry of the optical indicatrix from English into German.[43] Ambronn also developed a number of techniques to make polarized light microscopy more generally useful in biology. In 1889 and again in 1890, Ambronn left Leipzig to spend some time at the Naples Zoological Station. There he met a host of new colleagues who were eager to see what polarization microscopy could do for the station's marine anatomical and taxonomic work; in turn, the *Stazione*'s biologists helped Ambronn broaden his experience of biological materials to include both invertebrate and vertebrate nerve and muscle tissues. The marine zoologists at Naples also shared what they had learned about histological staining and fixative chemicals. From then on Ambronn pursued the optical effects of a growing range of solvents and histological chemicals on a wide range of biological tissues. His most important technical innovation was in the use of gold and silver (gold chloride and silver nitrate) stains to intensify the optical anisotropy of otherwise weakly birefringent objects, a technique would eventually be known as "dichroic staining."

By the end of the nineteenth century Ambronn had established a reputation as the unparalleled expert in polarized light microscopy, and a pioneer in dichroic staining. Not only did Ambronn try to address biologists' concerns about the physical-chemical effects of staining and

42. "Botanische Vorlesungen an den deutschen Universitäten und andere Hochschulem im Sommer 1889," *Deutsche botanische Monatsschrift: Organ für Floristen, Systematiker und alle Freunde der heimischen Flora* 7 (1889): 63. Leipzig Univeristy lists historical courses going back to 1814; see "Übersicht der Lehrveranstaltungen von Hermann Ambronn an der Universität Leipzig (Sommersemester 1883 bis Wintersemester 1899)," accessed February 28, 2016, http://histvv.uni-leipzig.de/dozenten/ambronn_h.html.

43. Lazarus Fletcher, *Die optische Indicatrix, eine geometrische Darstellung der Lichtbewegung in Krystallen*, trans. Hermann Ambronn and Walter König (Leipzig: Johann Ambrosius Barth, 1893).

fixation: his research was being conducted at the same time as microscope manufacturers were reaching the theoretical resolution limits of ordinary light microscopes. This timing changed Ambronn's fortunes considerably, and would at last land Ambronn the prestigious job he had sought for so long. In 1899, Ernst Abbe (1840–1905) — one of the founders of modern optics, the inventor of apochromatic lenses, and the research director of the Carl Zeiss optical works — established a new professorship in scientific microscopy at the University of Jena, and selected Ambronn for the job that summer.[44] In 1902 Abbe poured further funds into the university, expanding Ambronn's professorship into an entire institute for microscopy.[45] Abbe then chose Ambronn to be his successor at Carl Zeiss's microscopy division, giving Ambronn a leading role at Germany's most important microscope manufacturer, until he left that position in 1906.[46]

c. *Colloids, scientific microscopy, and the* Wiener Mischkörper

At Jena and Carl Zeiss, Ambronn's work became less and less grounded in botany as his new colleagues encouraged him to engage more directly in mathematics, optics, and colloid chemistry. He also began rely on inorganic exemplary materials, namely colloidal gold and alumina, because these were the materials his colleagues were interested in. In the previous century, Ambronn, Nägeli, and Schwendener had all tried to validate micellar theory by highlighting and amplifying birefringence phenomena, often using relatively complex organic materials. In the first decades of the twentieth

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44. Albert Frey, "Hermann Ambronn," *Kolloidchemische Beihefte* 23 (1927): 1–5. On Zeiss, Abbe, and their development of scientific microscopy before 1890, see Stuart M. Feffer, "Ernst Abbe, Carl Zeiss, and the Transformation of Microscopical Optics," in *Scientific Credibility and Technical Standards in 19th and Early 20th Century Germany and Britain*, ed. Jed Z. Buchwald (Dordrecht: Kluwer, 1996), 23–66; and, in the same volume, David Cahan, "The Zeiss Werke and the Ultramicroscope: The Creation of a Scientific Instrument in Context," 67–115, especially 82–86.

45. Hermann Ambronn, "Ueber Institute für wissenschaftliche Mikroskopie und deren Aufgaben," *Zeitschrift für wissenschaftliche Mikroskopie und mikroskopische Technik* 24 (1907): 1–12.

46. Albert Frey et al., "Hermann Ambronn zum siebzigsten Geburtstage (11. August 1926)," *Naturwissenschaften* 14, no. 33 (August 13, 1926): 766.

century, Ambronn found that validation by learning how to control, measure, and quantify birefringence, using simple inorganic materials. These new skills allowed him in 1916–17 to bring to bear new mathematics and theories from ether physics, what would become known as the "Wiener mixed-body theory" or Wiener's "*Theorie des Mischkörpers*" — a mathematical formula that allowed Ambronn to visually and analytically decompose a heterogeneous colloid into its component parts. Ambronn's friends and colleagues at Zeiss were also responsible for seeking broader moral and experimental support for Ambronn's micellar theory, as they promoted it as a new and practical way of understanding and studying colloidal structure.

Ambronn was the last of a quartet of scientists whom Abbe recruited to Zeiss in the 1890s to push scientific microscopy beyond its existing methodological and epistemological limits. Together with August Köhler (1866–1948), Henry Siedentopf (1872–1940), and Richard Zsigmondy (1865–1929), Ambronn developed new sample preparation methods, new interpretive approaches, and a traveling pedagogical program aimed at promoting new techniques — and the Zeiss microscope catalogue — to scientists and physicians across the German-speaking academy.[47] At the *Ambronnfest* in 1926 Köhler gave a sense of what it meant for Ambronn to have space to focus on scientific microscopy, rather than botany or physics alone:

> One must ask: where is the limit up to which one can still interpret the images of optical instruments in the old and familiar way? Is there a sharp boundary or a gradual transition between the area where, on the one hand, a certain differentiation of shapes and sizes is possible, and on the other, where the picture supplies only more or less questionable signs of a finer structure? What can else can you conclude from such evidence with security? On what circumstances does the location of this limit depend?[48]

47. The course covered not just basic operation and optical theory in microscopy, but also techniques for counting and measurement, different approaches to illumination, the intricacies of polarized light microscopy, technique in photo-micrography, as well as special considerations in mineralogy, colloid chemistry, and biology. Albert Frey gives a full list of locations in, "Hermann Ambronn," *Berichte der deutschen botanischen Gesellschaft*, 63.

48. Albert Frey et al., "Hermann Ambronn zum siebzigsten Geburtstage," 766; Hubert de Martin and Waltraud de Martin, *Vier Jahrhunderte Mikroskop* (Wiener Neustadt: Weilburg-Verlag, 1983), 152.

For Köhler, the disciplinary and technological imperative of scientific microscopy meant not only asking how far microscopic technique could be pushed, but how far microscopic *interpretation* could go, all while confronting the resolution limits of ordinary light microscopy. Ambronn had an interpretive framework and a theoretical agenda, and he was technically skilled, but he would need additional help to strengthen the link between polarized light microscopy and his micellar theory.

While pedagogy and the traveling course were essential to the Zeiss group's success, it was the new microscopes the group invented that made them into scientific celebrities: in 1904 Köhler invented one of the earliest ultraviolet microscopes, and in 1903 Zsigmondy and Siedentopf developed the slit-ultramicroscope, which allowed indirect observation of colloidal particles that were much smaller than the wavelength of visible light.[49] The slit-ultramicroscope's transformation of colloid chemistry would win Zsigmondy the Nobel Prize in 1926, and it would be used by Jean Perrin in 1909 to prove Einstein's atomic theory of Brownian motion.[50]

At the same time, Ambronn's new colleagues at Jena pushed him to reconsider the micellar theory, polarized light microscopy, and colloid chemistry together, in a way that he had not since 1889. Zsigmondy, especially, encouraged Ambronn to revisit micellar theory and colloid chemistry after he saw an article on gold and silver staining Ambronn wrote in 1896.[51] As a glass chemist, Zsigmondy had long been interested in the way trace amounts of gold could create both a dramatic "cranberry" red when used in decorative glassware, and a deep purple when used to decorate

49. On the history of the Carl Zeiss Werke and Zsignmondy and Siedentopf's invention of the slit ultramicroscope, see David Cahan, "The Zeiss Werke and the Ultramicroscope."

50. On Jean Perrin, the Einstein–Smoluchowski theory of Brownian motion, and the ultramicroscope, see Charlotte Bigg, "Evident Atoms: Visuality in Jean Perrin's Brownian Motion Research," *Studies in History and Philosophy of Science Part A* 39, no. 3 (September 2008): 312–22; and, "A Visual History of Jean Perrin's Brownian Motion Curves," in *Histories of Scientific Observation*, ed. Lorraine Daston and Elizabeth Lunbeck (Chicago: University of Chicago Press, 2011), 156–79.

51. Hermann Ambronn, "Ueber Pleochroismus pflanzlicher und thierischer Fasern, die mit Silber- und Goldsalzen gefärbt sind," *Berichte über die Verhandlungen der königlich sächsischen Gesellschaft der Wissenschaften zu Leipzig, mathematisch-physische Klasse* 48 (1896): 613–28,

ceramics.[52] Colloidal gold had long been known to have unique optical properties, including its brilliant red color (even in very dilute solutions) and its ability to scatter light in a "Tyndall cone," but Zsigmondy wanted to know exactly why gold was capable of this. In the 1896 article, as part of his research into dichroic staining, Ambronn had suggested that gold in solution was made up of small crystals, and that the alignment of these gold crystals could cause unique optical (dichroic) effects when used as a biological stain.[53] As soon as Ambronn joined Zsigmondy at Zeiss, the two began to pursue different ways of determining the exact size and optical nature of gold particles in both colloidal and non-colloidal solutions (see Figure 3.1).[54] Encouraged by Zsigmondy, Siedentopf, Köhler, and the scientific culture within Zeiss, Ambronn threw himself into colloid chemistry, becoming thoroughly invested in Zsigmondy's broader project to find a theory of colloidal structure and behavior. Together with Siedentopf, Ambronn and Zsigmondy each worked on the optical study of finely dispersed metals in solution. For Ambronn this would be a subtle, but significant departure from his previous approaches to dichroic staining. In the 1890s he had been thinking about gold and silver staining merely as a way of enhancing dichroism and other birefringence effects. At Jena, Ambronn and his team were trying to discern the nature and properties of the colloidal gold and silver particles themselves.

Ambronn's first significant breakthrough in the structure of colloidal metals came in 1910 — not through gold or silver, but through a study of colloidal alumina, or *"Tonerde."* Alumina was a sharp, accidental departure from Ambronn's usual laboratory materials. It came from his reaction to a

52. David Cahan, "The Zeiss Werke and the Ultramicroscope," 90–92; Milton Kerker, "Zsigmondy, Richard Adolf," in *Complete Dictionary of Scientific Biography*, vol. 14 (Detroit: Charles Scribner's Sons, 2008), 632–34. On colloidal gold in Purple of Cassius see L. B. Hunt, "The True Story of Purple of Cassius," *Gold Bulletin* 9, no. 4 (1976): 134–39.

53. Richard A. Zsigmondy, "Nobel Lecture: Properties of Colloids (1926)," in *Nobel Lectures, Chemistry 1922–1941* (Amsterdam: Elsevier, 1966), 45–57, on 52.

54. Hermann Ambronn and Richard Zsigmondy, "Ueber Pleochroismus doppelbrechender Gelatine nach Färbung mit Gold- und Silberlösungen," *Berichte über die Verhandlungen der königlich sächsischen Gesellschaft der Wissenschaften zu Leipzig, mathematisch-physische Klasse* 51 (1899): 13–15; Zsigmondy discusses this further in *Zur Erkenntnis der Kolloide: über irreversible Hydrosole und Ultramikroskopie.* (Jena: Gustav Fischer, 1905), 171–72.

paper in 1907, given by the organic chemist Hans Adolf Wislicenus and the botanist Ludwig Jost at the annual meeting of the *Gesellschaft deutscher Naturforscher und Ärzte* (GDNÄ). Alumina (or aluminum oxide) could be induced to form fiber-like structures, which Wislicenus and Jost called "*Tonerdefasern*."[55] The the two had hoped that they could compare organic fiber growth in plants and animals to the growth of inorganic alumina "fibers," which appeared to grow by a process of colloidal adsorption (*i.e.,* a process of accretion).[56] Within their larger analysis, Jost compared the colloidal alumina's structure to tabasheer, a flaky, mealy, silica resin secreted by some species of bamboo at its joints. Then Jost made a series of claims that Ambronn would soon seize upon:

> The comparison between starch granules and the growing alumina is not merely a superficial analogy between the two structures, which is apparent from the complete agreement of the optical properties of both structures: namely, the alumina is birefringent, and using the *Rot I* compensator it shows the exact same color patterns as the eccentric part of a canna lily starch granule. The cause of this birefringence in the alumina is a lamellar structure, *i.e.* originating from an anisotropic arrangement of isotropic particles. The birefringence disappears when placing the clay in water or xylene, and returns after the water evaporates, similar to what [Ferdinand] Braun observed in tabasheer with xylene. Incidentally, according to [Otto] Bütschli tabasheer can be considered structureless.[57]

Jost essentially made a number of claims about starch granules and birefringence that Ambronn would have been familiar with; these claims also came from areas of botany and colloid chemistry that Ambronn had recently become acquainted with at Jena. However, Jost suggested that it was the anisotropic arrangement of isotropic particles that caused the alumina fibers' birefringence — the opposite to what Ambronn, Nägeli, and Schwendener had been claiming in the nineteenth century. Their micellar theory held that it was the isotropic arrangement of anisotropic particles, *i.e.* the micelles, that caused birefringence effects in starch granules. That the micelles were birefringent and

55. For some reason Wilkie translates *Tonerde* and *Tonerdefasern* as "'clay-fibres,' which gives no clue as to the nature of the structures concerned"; he continues, "*Tonerdefasern* are in fact fibres of aluminium hydroxide." Most dictionaries agree that "*Tonerde*" is alumina or aluminum oxide, not aluminum hydroxide. cf. J. S. Wilkie, "Nägeli's Work on the Fine Structure of Living Matter," 232.

56. Hans Wislicenus, "Ueber die faserähnliche gewachsene Tonerde (Fasertonerde) und ihre Oberflächenwirkungen (Adsorption)," *Zeitschrift für Chemie und Industrie der Kolloide* 2, no. 2 Supplement (March 1908): 9–20.

57. *ibid.,* 15. On the *Rot I* compensator, see Appendix A. Canna lilies produce very large starch granules in their roots.

had optical anisotropy had been Ambronn's central claim in the 1880s, when he had defended Nägeli and Schwendener against von Ebner's critiques.

The essential clue within Wislicenus and Jost's 1910 paper was that a material's birefringence could disappear when placed in water or xylol — a clue that Ambronn had either forgotten, ignored, or did not know about before 1910. For Ambronn, Jost's comparison of the alumina fibers with tabasheer brought to mind a more familiar kind of siliceous substance: diatom shells, which Ambronn would have familiar with as a test-object for checking the resolution and alignment of microscopes. Diatom shells are strongly birefringent, and Ambronn now remembered (perhaps from the first pages of von Ebner's monograph) that in 1863 Max Schultze had found that diatoms' birefringence disappears when they are embedded in Canada balsam, a glue that was commonly used both for making permanent microscope specimen slides and in cementing compound lenses. For half a century this disappearing birefringence was considered proof that diatom shells were birefringent only by virtue of their grid-like, porous structure, and not caused by any inherently birefringent structure within the silica that made up the shell; as a result, neither Nägeli, Schwendener, nor Ambronn had thought this was worth commenting on.[58] Now, however, Ambronn tried something different, prompted by Jost's suggestion that the birefringence of alumina fibers was eliminated when they were immersed in either xylene or water: Ambronn decided to see if the birefringence of diatom shells disappeared when immersed in other fluids. Ambronn found not only that some fluids could make the diatoms' birefringence disappear, but also that others could merely weaken it:

58. That neither Nägeli nor Ambronn ever mentioned this phenomenon before 1910 suggests that they did not think it was worth mentioning, despite the fact that it had been known as early as 1859. This is especially notable since Nägeli and Schwendener heavily promoted the use of diatoms as microscope test-objects in *Das Mikroskop* in 1867. See Max Schultze, "Die Structur der Diatomeenschale," *Verhandlungen des Naturhistorischen Vereines der preussischen Rheinlande und Westphalens* 20 (1863): 1–41; and Victor von Ebner, *Untersuchungen über die Ursachen der Anisotropie organisirter Substanzen*, 2–3. On diatoms as test-objects see Carl Nägeli and Simon Schwendener, *Das Mikroskop*, 133–35; Jutta Schickore, "Test Objects for Microscopes," *History of Science* 47, no. 2 (June 2009): 117–45; and Randy O. Wayne, *Light and Video Microscopy* (Academic Press, 2013), 71 and 319. Wayne points out that the English diatom enthusiast J. D. Sollitt proposed using diatoms as microscopy test objects as early as the 1840s.

> The aforementioned phenomena can only be observed, however, if the [diatom] shells are surrounded by a [fluid] medium with a different refractivity. The greater the difference between the two refractive indices, the greater is the resulting phase difference. At the same time, the sign [of birefringence in the diatom shell] remains the same, whether the difference of the refractive indices is positive or negative. The anisotropy will disappear completely, however, if this difference is equal to zero. One can observe, for example, that when the shells are placed in Canada balsam or cedarwood oil, there is no noticeable brightening [*i.e.*, no birefringence] between crossed Nicols…[or] one can observe the shells in air or in red arsenic — in both cases the difference in refractive index [compared to the diatom shell] is 0.5 or more, and thus the brightening is strong. It is quite considerably weaker if one examines the shells in water or 1-bromonapthaline; in these two cases the difference in refractive index is only about 0.2.[59]

All of Ambronn's work with staining technique in polarized light microscopy had, until this point, been aimed at increasing contrast, color, and optical anisotropy. Now he was pursuing a technique that, for all intents and purposes, was aimed at reducing or eliminating birefringence, rather than enhancing it.

Quantified refractive indices had been brought to Ambronn's attention by the Leipziger physicist Otto Wiener (1862–1927), with whom Ambronn had become acquainted by 1905; the two struck up a close professional partnership, and exchanged manuscripts and exchanged research advice for the rest of their lives.[60] In 1904 Wiener had developed what would soon become known as the "Wiener mixed-body theory," while seeking a theory that could explain the behavior of light when two materials of different electromagnetic properties (diaelectric, ε) were mixed — a problem prompted by questions about the optical behavior of very fine-grained photographic emulsions.[61] Working through 1909, Wiener developed two sets of equations that related the combined refractive indices for two idealized systems to the refractive index of each of their parts: a "lamellar" system of two materials stacked in alternating layers; and a more complex system of parallel cylinders or

59. Hermann Ambronn, "Ueber das optische Verhalten und die Struktur der Tonerdefasern," *Zeitschrift für Chemie und Industrie der Kolloide* 6, no. 4 (March 1910): 222–23.

60. "Nachlass Otto Wiener (1862-1927)," *Kalliope-Verbund* union catalog, accessed March 28, 2016, http://kalliope-verbund.info/de/eac?eac.id=117362751.

61. Otto Wiener, "Lamellare Doppelbrechung," *Physikalische Zeitschrift* 5, no. 12 (1904): 332–39; for some more detail on Lippmann and the issues surrounding thin photographic film emulsions, see Winston Kock, *Engineering Applications of Lasers and Holography* (New York: Plenum Press, 1975), 97.

"rodlets" of one material running through a medium of the second (Figure 4.4).[62] Until the outbreak of the First World War, Wiener hoped that by continuing to refine the mathematics he could create a generalized theory for the behavior of waves in any field or mixed medium, whether it be sound waves in the air or light waves in the ether.[63]

Ambronn realized that, even though Wiener's mathematics were based on abstract (and essentially fictional) models, they offered a new kind of mathematical justification for his idea of micelles as optically active particles that could be arranged and moved within their medium by external forces. Ambronn made the small leap to claim that micelles were, mathematically-speaking, Wiener rodlets and platelets: he had, after all, used the word "rodlet" (*"stäbchen"*) as a substitute for "micelle" in 1888.[64] It took an additional five years for Ambronn to fully grasp and rewrite the mathematics (as well as translate Wiener's use of dielectrics, rather than refractive index) to develop useful equations for the birefringence of a rodlet mixed-body,

$$n_e^2 - n_o^2 = \frac{\delta_1 \delta_2 (n_1^2 - n_2^2)^2}{(\delta_1 + 1) n_2^2 + \delta_2 n_1^2} \; ;$$

and for a platelet mixed body,

$$n_e^2 - n_o^2 = \frac{\delta_1 \delta_2 (n_1^2 - n_2^2)^2}{\delta_1 n_1^2 + \delta_2 n_2^2} \; ,$$

62. Otto Wiener, "Zur Theorie der Stäbchendoppelbrechung," *Berichte über die Verhandlungen der königlich sächsischen Gesellschaft der Wissenschaften zu Leipzig, mathematisch-physische Klasse* 61 (1909): 113–16.

63. Otto Wiener, "Die Theorie des Mischkörpers für das Feld der stationären Strömung," *Abhandlungen der königlich sächsichen Gesellschaft der Wissenschaften, mathematisch-physischen Klasse* 32, no. 6 (1913): 509–604.

64. See note 40, above.

that could relate the refractive index for the extraordinary ray of the whole mixed-body system (n_e), and the ordinary ray of the mixed-body (n_o), in relation to the volume of the particles (δ_1) and the medium (δ_2) and the average refractive index of the particles and medium (n_1 and n_2, respectively).[65] As a mathematical consequence of Wiener's mixed-body models, rodlet birefringence is always positive relative to the optical axis, while platelet birefringence is always negative relative to the optical axis. However, the *intensity* of the birefringence in both cases could vary: this manifests itself in the brightness of the object under crossed Nicols, and in the intensity and types of interference patterns visible under the polarized light microscope.

Ambronn's adaptation of Wiener's mixed-body equations in 1916 allowed him to mathematically decompose the mixed body, separating its solid, micellar parts from the fluid suspension. Nägeli, Schwendener, and Ambronn alike had spent decades in vain trying to convince others to imagine oriented, birefringent particles that could explain both optical phenomena of plant matter and the invisible structure of the same. With the Wiener mixed-body theory, Ambronn could now argue that the individual parts of colloids could be seen separately — or at least, their optical properties could be decomposed and analyzed separately.

Actually using the equations to inform laboratory work proved relatively simple. The procedure Ambronn developed involved immersing samples in fluids of known refractive index, which changed the refractive index of the medium (n_2) as the fluid penetrated; Ambronn would later call this his "immersion method" or "imbibition method."[66] Once the sample had sufficiently imbibed the new fluid, it was examined under crossed polarizers and a quartz wedge compensator (invented by Siedentopf in 1906) to precisely measure the sign and the intensity of birefringence,

65. Hermann Ambronn, "Ueber das Zusammenwirken von Stäbchendoppelbrechung und Eigendoppelbrechung, I," *Kolloid-Zeitschrift* 18, no. 3 (April 1916): 90–97.

66. Hermann Ambronn and Albert Frey, *Das Polarisationsmikroskop: Seine Anwendung in der Kolloidforschung und in der Färberei*, Kolliodforschung in Einzeldarstellungen, Bd. 5 (Leipzig: Akademische Verlagsgesellschaft, 1926).

$n_e - n_o$. The resulting graphs (Figure 4.5), and specifically the lowest point on each curve, would then show what proportion of the birefringence for which the micelles was responsible; curve *A* on Figure 4.5 shows an example of rodlet mixed-body birefringence where the rodlet-shaped micelles themselves are positively birefringent, and curve *C* shows an example of rodlet mixed-body birefringence where the rodlet-shaped micelles themselves are negatively birefringent. (The curves for both types of platelet birefringence would be mirrored across the *x* axis, with the curve facing down.) At this point, when the effects of the medium are eliminated and $n_2 = 0$, the optical properties of the micellar particles alone could be studied, both in its resting state or under stress. Thus Ambronn could prove that micelles possessed their own "intrinsic" birefringence — weak, strong, positive or negative — independent of the birefringence of the whole material system of rodlets or platelets.

In Ambronn's newly developing terminology, the birefringence of the overall mixed-body, the "form birefringence" ("*Formdoppelbrechung*") could be decomposed to reveal the "intrinsic birefringence" ("*Eigendoppelbrechung*") of the crystalline micelles.[67] (In Figure 4.5, curve B shows a case where *only* intrinsic rodlet birefringence is responsible for the total birefringence; the medium has no effect, and there is no form birefringence.) In arguing that the birefringence of heterogeneous materials was due to the way a system's parts — the medium and the micelles — worked together, Ambronn was making a genuine departure from his and Nägeli's arguments in the nineteenth century, which relied only on the hypothetical movements of birefringent micelles and molecules. Ambronn even had a name for the birefringence of whole systems, the "total birefringence" or "*Gesamtdoppelbrechung*," though most preferred the slightly narrower concept of form birefringence.

67. "*Eigendoppelbrechung*" was Ambronn's term; his student Albert Frey coined "*Formdoppelbrechug*" in 1925; see "Doppelbrechung der Dispersoide," *Kolloidchemische Beihefte* 20, no. 6 (January 1925): 209–43. In English the term "crystalline birefringence" was sometimes used instead of "intrinsic birefringence."

Ambronn's theory and method in combination aimed at separating out the intrinsically birefringent parts out from the total optical effects.

Ambronn synthesized all of this work in polarized light microscopy with the Wiener mixed-body theory in a series of three articles in *Kolloid-Zeitschrift* in 1916–17, liberally including references to Carl Nägeli and the longer history of the micelle. (This appeal to historical precedent might be similar to the appeals made in 1900 by de Vries, Correns, and Tschermak about Mendel's laws: the half-century that separated the modern re-discoverers and the original geniuses became elided by their reference to historical names and terminology.[68]) Near the end of Ambronn's third part, he reminded readers that,

> Over fifty years ago [Ernst] Brücke and [Carl] Nägeli traced the anisotropy of fibers in plant and animal bodies to molecular complexes running in the same direction, and Nägeli, especially, attempted to ground this conception through more exact work; he later called these particles "micelles" and then called his vision as well as his theory the hypothesis of crystalline micelles, or in short the micellar hypothesis.[69]

And yet between Nägeli and Ambronn, those fifty years made for a very wide scientific gulf. Ambronn's micellar theory consisted of birefringent crystalline micelles whose optical appearance was modified by the medium in which they were embedded. Ambronn never used Nägeli's Newtonian forces, he moved away from thinking solely in terms of moving micelles, and he avoided Nägeli's distinction between organic crystalloids versus inorganic crystals. Ambronn's use of laboratory materials was also a significant departure: rather than rely on organic and recently living materials to speak to the organic world, Ambronn used prepared tree resins, gelatin, rare earth metals, clays, and in the 1916–17 essays nitrocellulose, hoping to demonstrate a more fundamental theory of matter and colloidal structure. These materials, Ambronn's new position, and his new colleagues all conspired to make Ambronn an expert in one particular aspect of colloid chemistry. *Kolloid-*

68. Jan Sapp, *Genesis: The Evolution of Biology* (Oxford: Oxford University Press, 2003), chapter 11.

69. Hermann Ambronn, "Ueber das Zusammenwirken von Stäbchendoppelbrechung und Eigendoppelbrechung, III," *Kolloid-Zeitschrift* 20, no. 4 (April 1917): 182.

Zeitschrift was also a scientific journal which demanded quantitative measurement of the material world, and which also allowed for many different ideas of colloid theory to co-exist.

Zsigmondy, Siedentopf, and Köhler all recognized that Ambronn's newly articulated micellar theory — that birefringent particles interacted with their fluid medium to create optical effects under polarized light in predictable and quantifiable ways — had immense potential in colloid chemistry for studying the relationship between colloidal particles and the colloidal medium. The trio immediately began to recruit supporters and experimentalists to find other ways of proving that Ambronn's theory of birefringent micelles could apply across all of colloid chemistry, not just in biology. In fact, hidden within Ambronn's essays were signs of his technical debts to the trio. Zsigmondy had encouraged Ambronn all along to marry his micellar theory to colloid chemistry; Siedentopf had invented the quartz wedge compensator that allowed for easier, more precise measurement of the intensity of birefringence; and Köhler had recommended the use of a mercury arc lamp for steady illumination at known wavelengths.[70] (Having made his best argument for the existence of the micelle, Ambronn's research and writing essentially concluded in 1917: he had proven the existence of micelles, at least to himself.) All four microscopists saw x-ray crystallography as the ultimate vindication of Ambronn's micellar theory. As Ambronn wrote at the end of his 1917 paper:

> It would be most desirable if the spatial anisotropy of the particles, and their transition from a random arrangement to a more oriented arrangement, could be proven by a different method. It stands to reason to think of irradiation by x-rays…[and] my hopes for success may lie in experiments using methods like those of Debye and Scherrer…Unfortunately I currently lack the ability to carry out such experiments.[71]

70. Hermann Ambronn, "Ueber das Zusammenwirken von Stäbchendoppelbrechung und Eigendoppelbrechung, II," *Kolloid-Zeitschrift* 18, no. 6 (June 1916): 276.

71. Hermann Ambronn, "Ueber das Zusammenwirken von Stäbchendoppelbrechung und Eigendoppelbrechung, III," 185.

Zsigmondy had by this point left Jena for Göttingen (in 1907), where his new colleagues Peter Debye (1884–1966) and Paul Scherrer (1890–1969) had worked together in 1915 to develop a new method of x-ray crystallography. Debye and Scherrer's new technique was powder diffraction, and it was a relatively easy way to determine the dimensions, size and relative crystallinity of a solid substance, requiring relatively little careful specimen preparation (more about powder diffraction will be covered in the next section).[72] At the same time, Reginald Oliver Herzog (1878–1935), head of the recently-formed Kaiser Wilhelm Institute for Fiber Chemistry in Berlin, also enthusiastically endorsed Ambronn's theory in front of the *Chemische Gesellschaft* meeting at Breslau in 1920.[73]

The scientists who initially seized on micellar theory in the 1920s were clustered around the disciplines and problem areas in which Ambronn and his colleagues closely worked. A roster of these scientists vividly shows both the diversity and divisions within colloid chemistry, and that colloidists were just as often interested in developing instruments and techniques as they were in solving specific material problems. For example, Siedentopf and Zsigmondy saw Ambronn as having discovered something fundamental about the way colloids scatter light, and viewed Ambronn's micellar theory as a contribution to optics as much as to colloid chemical theory. For Debye and Scherrer, the micellar theory opened the door for x-ray crystallographic studies of some colloids — the numerous colloidal materials that were clearly not crystalline as a whole, but still had crystalline parts. Herzog was ultimately interested in the structure, behavior, and development of natural and artificial fibers, and he recruited a diverse, sometimes fractious group of physical chemists to his institute to pursue this. And Ambronn himself was now supervising a number of students working with polarized light

72. Richard Zsigmondy, "Persönliches und Sachliches zu Ambronns 70. Geburstage: Über die kristalline Natur der Teilchen in kolloidem Golde und deren Sammelkristallisation," *Kolloidchemische Beihefte* 23 (August 1926): 21–27.

73. R. O. Herzog, "Über einige Fragen der Faserstoffchemie," *Naturwissenschaften* 8, no. 34 (August 1920): 673–81; and R. O. Herzog, Willi Jancke, and Michael Polanyi, "Röntgenspektrographische Beobachtungen an Zellulose. II," *Zeitschrift für Physik* 3, no. 5 (September 1920): 343–48.

microscopy and Wiener's mixed-body theory, refining his past research on the birefringence of various model substances.[74]

As discussed above, the debate over the structure of fibers has been well documented in the historical literature, and, as Olby and Morawetz show, the scientific debate in the 1920s centered around the generation and interpretation of x-ray diffraction diagrams.[75] Herzog and the KWI for Fiber Chemistry in the 1920s advocated for a way of interpreting x-ray diffraction diagrams that suggested that cellulose micelles were very tiny, in the mid- to high-single digits of glucose molecules. Herzog and many other colloid chemists saw a small-micellar approach as a way to keep the prevailing physical chemical and colloid chemical theory closely aligned to the new x-ray technique. On the one hand, small micelles accommodated the limits of x-ray crystallography itself: a basic assumption in x-ray crystallography held that one could only accurately find the arrangement of atoms in a "unit cell," the smallest repeating crystal structure in the larger body. On the other hand, assuming that micelles were small had the benefit of allowing x-ray crystallographic studies of fibers to fit neatly within both colloidal theory and micellar theory, by considering the micelle and the unit cell as being the same entity. Olby and Morawetz essentially describe the intense debate among the x-ray crystallographers working on fibers as one over the size and internal configuration of fiber unit cells, with this period culminating in the endorsement of Ambronn's micellar theory by the chemists Herman Mark and Kurt Meyer in 1928. Outside of the Debye-Scherrer powder diffraction technique, x-ray crystallography at its best measured the distance between atoms within a single unit cell, and the crystallographers worked under the assumption that the rest of the fiber was merely a repetition of those unit cells. What were the dimensions of the micelle/unit cell, how many

74. A list of projects by Ambronn's students until his death is at the end of Albert Frey, "Verzeichnis der wissenschaftlichen Veröffentlichungen von Hermann Ambronn und seiner Schule," *Kolloid-Zeitschrift* 44, no. 1 (January 1928): 6–8.

75. Robert Olby, *The Path to the Double Helix*, chapter 3; Herbert Morawetz, *Polymers: The Origins and Growth of a Science* (New York: John Wiley & Sons, 1985), chapter 9.

molecules could fit within the micelle/unit cell, and how strong were the forces that held micelles/unit cells together into fibers — these all became the heart of the debate over the existence of long-chain macromolecules.

The atom-by-atom approach in x-ray crystallography achieved fine-structural detail, but the appeal of polarized light microscopy had long been in the realm of biological cell and tissue analysis, where atomic detail in angstrom-scale units was considered extravagant. Besides that, in biology one would need to know how different kinds of micelles were assembled into larger complexes, and x-ray crystallography promised to reveal only the internal structure of one unit cell. Practitioners of both x-ray crystallography and polarized light microscopy alike readily admitted that their methods were indirect, relative to the seemingly self-evident nature of ordinary light microscopy.[76] Although in the 1890s Ambronn may have had ambitions to explore the sub-microscopic realms of biology, his move into scientific microscopy subordinated actual biological structure to optical theory and microscopic practice. Once biologists actually began to use Ambronn's imbibition method to reveal micellar structures, they soon had to decide how they would approach both smaller and larger scales of organization. It also remained an open question whether x-ray crystallographic evidence could claim greater importance or epistemological status over evidence from polarized light microscopy, given the minute scales at which x-ray crystallography worked, and the basic methodological requirement for its samples to come in powdered or pure crystal form.

76. For example, Francis O. Schmitt, "The Ultrastructure of Protoplasmic Constituents," *Physiological Reviews* 19, no. 2 (1939): 271.

d. Albert Frey-Wyssling, cell wall structure, and the "principle of repetition"

The grand synthesis of polarized light microscopy and x-ray crystallography — of the micellar theory and atomic structure — arrived in 1938, with the publication of Albert Frey-Wyssling's *The Sub-Microscopic Morphology of the Protoplasm and its Derivatives.* The book was a resounding success, even in its first, German edition as volume 15 of the *Protoplasma-Monographien* series, and it would later be translated into English, Russian, Spanish, and even Italian (but, for some reason, not French).[77] The book opened with the table "*Das Reich der Morphologie*," attempting, at a glance, to address spatial scale, technique or technological requirement for observation, "morphological hierarchy," and even disciplinary divisions (Figure 4.6).[78] The many elements and theories that Frey-Wyssling assembled into this table were meant to show how invisible, tiny parts could make up whole organisms, in a series of sensible organizational steps. It is a synthesis that has more or less persisted to today, with two major exceptions on the fourth row of the morphological hierarchy: "fine structure," addressed via micellar theory and polarized light microscopy. This table elides the fact that even by 1938, Frey-Wyssling was on the verge of giving up the micellar theory as Ambronn had developed it, leaving a significant gap in not only the table, but also in biologists' conceptual and imaginative universe. This last section will show how Frey-Wyssling found a way through his "principle of repetition" to reconcile the micellar theory with Hermann Staudinger's theory of long chain molecules — an optical theory with a chemical one.

A native of Zürich, Albert Frey (later Frey-Wyssling, after he married Margarit Wyssling in 1928) was a quintessential product of the intensely physicalist approach to botany that had taken hold at the *Eidgenössische Technische Hochschule* (ETH) in Zürich at the beginning of the twentieth

77. Albert Frey-Wyssling, *Lehre und Forschung*, 170.

78. Albert Frey-Wyssling, *Submikroskopische Morphologie des Protoplasmas und seiner Derivate*, Protoplasma-Monographien, Bd. 15 (Berlin: Gebrüder Borntraeger, 1938), 4–5.

century. He was sent to Jena in 1924 by Carl Schröter, head of the ETH's Institute for General Botany; in less than two years Frey became a devoted follower of Ambronn, following his rising star in the mid-1920s to great fame.[79] Like Ambronn before him, Frey's education took him through a unique and very high-level array of botany and physics laboratories — but unlike Ambronn, Frey was able to experience most of his education in one place, the ETH. Wilhelm J. Schmidt later wrote that "Frey-Wyssling had the luck to have been under the instruction of the greatest masters: (the crystallographer) Paul Niggli, Hermann Staudinger, Paul Scherrer, Hermann Ambronn, while I as a solitary wanderer had to cut my own path through the undergrowth."[80] Scherrer and Debye had both arrived at the ETH from Göttingen in 1920, and the colloid chemist and plant physiologist Georg Wiegner had long been an important presence in shaping plant studies at the ETH since 1913. In short, Frey-Wyssling's education, and his own research style after 1932, gave him a privileged position to understand and synthesize many different corners of what he called the "sub-microscopic morphology of the protoplasm and its derivatives."

Whereas Nägeli had imaginatively applied the micellar theory to explain all manner of plant physiological phenomena, Ambronn understood micelles only as an underlying structure that could explain certain optical phenomena; both Ambronn and his colleagues at Zeiss had seen Nägeli's extravagant hypothesizing as the reason why most botanists rejected micelles in the 1880s.[81] Frey was not so limited, and his research and writing through the 1950s shows a dogged determination to describe, in as great detail as possible, actual biological structures: the bulk of his research into the 1950s centered on the fine structure of cell walls, cellulose fibers, and chloroplasts. Initially, Frey's work at Jena looked a lot like Ambronn's work in the 1890s: a paper on dichroic staining of fibers,

79. Albert Frey-Wyssling, *Lehre und Forschung,* 44–45.

80. W. J. Schmidt, "Aus meiner Werkstatt," *Bericht der oberhessischen Gesellschaft für Natur- und Heilkunde zu Gießen, neue Folge, naturwissenschaftliche Abteilung* 33, no. 4 (1964): 217–37.

81. Richard Zsigmondy, "Persönliches und Sachliches zu Ambronns 70. Geburstage," 22.

and a paper on the micellar structure of gelatin.[82] More importantly, however, Frey completed a short textbook on polarized light microscopy, grounding its use in colloid chemistry more broadly.[83] Ambronn had begun the textbook, *The Polarization Microscope: Its Application in Colloid Research and Dyeing*, at the urging of Zsigmondy, who wanted to include it in his monograph series on methods in colloid chemistry. According to Frey, Ambronn had finished only one part on the crystallinity of micelles, and lost interest in the rest.[84] Frey worked to modify the Wiener mixed-body equations to work in a larger variety of real colloidal systems: if the micellar system was not quite like an ideal rodlet or platelet mixed-body, Frey found that rodlet- and platelet-shaped micelles could be simulated by pouring or stirring the colloid, the latter being the more practical in most laboratory situations (Figure 4.7). As Frey worked, Ambronn regaled him with tales of the old days with Pfeffer, Nägeli, and Schwendener, caring nothing for the "scrapping for priority" in which the younger biologist was caught up.[85] Indeed several features of the textbook show how little Ambronn had evolved since his struggles in the previous century: for example, the instrument it discussed for creating and measuring stress in colloids was identical to one Ambronn used in 1892, itself similar to the one von Ebner had used a decade before that.[86] In his 1984 autobiography, Frey-Wyssling never explained exactly why he became so enthusiastic about Ambronn or his theories, or why he had worked so hard in the 1920s to tie his own name to Ambronn's.[87] Whatever the case, he became the custodian of Ambronn's legacy, arranging for the *Ambronnfest* in 1926, writing obituaries in four

82. Albert Frey, "Doppelbrechung der Dispersoide"; and, "Zur Frage nach der Ursache des Dichroismus gefärbter Fasern," *Naturwissenschaften* 13, no. 19 (1925): 403–6.

83. Hermann Ambronn and Albert Frey, *Das Polarisationsmikroskop*.

84. Albert Frey-Wyssling, *Lehre und Forschung*, 48–51.

85. *ibid.*

86. Hermann Ambronn and Albert Frey, *Das Polarisationsmikroskop*, 156; compare with the instrument von Ebner describes in *Untersuchungen über die Ursachen der Anisotropie organisirter Substanzen*, 37.

87. Albert Frey-Wyssling, *Lehre und Forschung*, 46–52.

journals, and even picking up a project to republish excerpts Carl Nägeli's writings on micellar theory for *Ostwald's Klassiker der exakten Wissenschaften*.[88]

But keeping the legacy didn't mean stopping where Ambronn had. For Ambronn it had been enough to say that cell walls were optically anisotropic because they were composed of crystalline micelles of cellulose; Frey wanted to know more about how the cellulose micelles were arranged, what direction they were pointed in, and what their arrangement could say about the growth and the mechanical strength of plant fibers. After Ambronn's death Frey returned to the ETH to continue the research on fiber structure that he had begun in Jena, learning and using the Debye-Scherrer powder diffraction technique of x-ray crystallography to complement his own polarized light microscopy.[89] While polarized light microscopy was still the faster way of finding the overall alignment and orientation of the micellar structure of fibers, Frey needed x-ray diffraction images to measure the spaces in between the cellulose micelles. The Debye-Scherrer method allowed Frey to not only measure the average dimensions of each micelle, but more crucially to locate and measure the "intermicellar space," showing whether the micelles were loosely or tightly packed together.[90] In order to make the intermicellar spaces visible by x-ray diffraction, Frey used the same heavy metal stains Ambronn had pioneered in the 1890s, following Ambronn's belief that the gold and silver deposits would surround each micelle, producing an intense optical anisotropy (Figure 4.8). The resulting schemata of cell wall structures that Frey was able to produce were detailed pictures of large portions of plant cell walls — hemp, flax, cotton, ramie, as well as some specific cell types like bast

88. *Die Micellartheorie von Carl Nägeli*, ed. Albert Frey, see note 37, above. On Ostwald's series and the meaning of "Classics" see Richard Staley, *Einstein's Generation: The Origins of the Relativity Revolution* (Chicago: University of Chicago Press, 2008), 353–54.

89. Frey-Wyssling, Albert. Briefe. HS 0443:1368–23, and HS1369: 12–16. Hochschularchiv der ETH Zürich.

90. Albert Frey, "Die submikroskopische Struktur der Zellmembranen," *Jahresbücher für wissenschaftliche Botanik* 65 (1926): 195–223; "Der submikroskopische Feinbau der Zellmembranen," *Naturwissenschaften* 15, no. 37 (September 16, 1927): 760–65; and, "Das Reich des Ultramikroskopischen in der Biologie," *Protoplasma* 4, no. 1 (May 1928): 139–54.

(phloem), tracheid, and sieve tube element — drawn to give the a sense of how individual cellulose micelles arranged to create the cell walls that were already barely visible under the ordinary light microscope (Figure 4.9).

In the late-1920s and through the 1940s, fine structural research in biology was characterized by descriptions of the alignment and orientation of micelles, descriptions of the specimen's optical behaviors, and measurements of the sizes of both the micelles and the intermicellar spaces. For example, Frey-Wyssling's article on the cell wall structure of *Chaetomorpha* algae deployed a visual system that included: photomicrographs of the algae taken under crossed polarizers, graphs of total birefringence using the imbibition method, schematic diagrams showing the arrangement of micelles in the different layers of the cell wall, and reproductions of x-ray diffraction diagrams.[91] The micellar diagrams were especially important, both because they put the linear measurements achieved by x-ray diffraction in the context of the larger cell wall structure. These diagrams showed how different parts of the cell wall (or any other micellar structure) behaved optically, and how the interactions of the parts produced the optical effects that were actually visible in the polarized light microscope. The argumentative, even predictive value of micellar diagrams gave these relatively simple graphical forms the power to make micelles and their arrangements more real than a photo-micrograph or a simple verbal description ever could.

This particular way of depicting micellar structures, especially of circular or cylindrical structures like fibers, was a heuristic tool Frey had developed to help explain the relationship between micellar shape and micellar arrangement in complicated, three-dimensional objects. The dashes expressed the individuality of micelles in larger structures, and, in combination with index ellipses and textual descriptions, gave an indication both of how the micelles were arranged and what

91. E. Nicolai and Albert Frey-Wyssling, "Über den Feinbau der Zellwand von Chaetomorpha," *Protoplasma* 30, no. 1 (February 1938): 401–13.

birefringence patterns to expect. The idea that micelles were moving, individual, crystalline units had been fundamental to Nägeli all the way back to 1858, and had been an important reason why Ambronn could connect Nägeli's theory to Wiener's mixed-body equations. Frey's representation of fine structure was genuinely new, however, and remarkably "realist" insofar as it expressed the existence, shape, and orientation of micelles at sub-microscopic scales. Through the late 1920s and '30s Frey would produce a growing number of these micellar diagrams, showing not only that micellar structures exist, but that they could exist in a variety of different ways that reflected the diversity within classes of materials, and across both species and cell types.

In the 1930s fiber chemists working at smaller scales were beginning to move towards a synthesis of micellar physics and polymer chemistry, with Kurt Meyer and Herman Mark pushing the idea that "chain molecules" ("*Kettenmolekülen*") could exist, but were essentially bundled up into crystalline units: "50–60 such chains, lying bundle-like and parallel with one another, make up a crystallite, which in conjunction can be described as Nägeli's 'micelle,'" Meyer wrote. "The micelles are oblong, at least about ten times long as they are thick."[92] The challenge within x-ray crystallographic studies of fibers was how to move from the elementary bodies — atoms bonded into molecules — to larger fiber structures (Figure 4.10). It was also not lost on Meyer that such a theoretical synthesis could bring physical chemistry closer to biology and physiology, in much the way Nägeli had envisioned in the 1870s:

> It now seems to us that it is right to see the essential elements of morphological structure in primary valence chains, and to examine the available facts from this point of view, which the until now has only been relevant in explaining the "micellar" nature of living tissues. With this, more relationships between physiological and molecular processes can yet be uncovered.[93]

92. Kurt H. Meyer, "Räumliche Vorstellungen über den Bau der Kohlenstoffverbindungen und ihre Verwendung in der Chemie der Hochpolymeren," *Kolloid-Zeitschrift* 53, no. 1 (October 1930): 13.

93. *ibid.,* 17.

Meyer made this statement at the eighth *Kolloid-Gesellschaft* congress in 1930, frustrating an already testy Hermann Staudinger, who had spent the previous eight years pushing a "pure" macromolecular view of polymers bound together by primary valences.[94] In contrast to Staudinger, whose insistence on his views were often given only in strong polemics, Meyer actively began to create models and schematic diagrams to connect measurements of atomic diameters to measurements of micellar dimensions. Although these models were a continuation of several different nineteenth century chemical modeling conventions, Meyer's emphasis — and his realism — lay in the measurement of the dimensions of cellulose.[95] Building on these arguments, the American botanist William Seifriz (1888–1955) suggested an even more brick-like model of micellar and molecular structure (Figure 4.11), which Meyer and Frey-Wyssling began to circulate widely through the 1930s.[96]

However, Frey-Wyssling became dissatisfied with Meyer and Mark's adoption of this relatively naïve version of Nägeli's micelles. At the height of the conflict between Staudinger, who advocated for macromolecules, and R.O. Herzog's x-ray crystallographers and colloid chemists, who advocated for smaller micelles, Frey-Wyssling proposed another compromise theory in 1935. He realized that Meyer and Mark's brick-like theory of fiber structure could not explain why the tensile strength of natural cellulose fibers was higher than that of artificial celluloid. At the same time, he

94. Hermann Staudinger, "Über hochpolymere Verbindungen," *Kolloid-Zeitschrift* 53, no. 1 (October 1930): 19–32. See also Yasu Furukawa, "Hermann Staudinger and the Emergence of the Macromolecular Concept," *Historia Scientiarum* 22 (1982): 1–18.

95. See the introduction for more on nineteenth century molecular modeling; *cf.* Eric Francoeur, "The Forgotten Tool: The Design and Use of Molecular Models," *Social Studies of Science* 27, no. 1 (February 1997): 7–40.

96. William Seifriz, "The Contractility of Protoplasm," *The American Naturalist* 63, no. 688 (September 1929): 410–34. Seifriz created this image in December 1928 by adapting the diagrams from Kurt H. Meyer, "Neue Wege in der organischen Strukturlehre und in der Erforschung hochpolymerer Verbindungen," *Naturwissenschaften* 16 (1928): 781–92. Meyer reprinted Seifriz's image (without attribution) in 1930, in Kurt H. Meyer, "Räumliche Vorstellungen über den Bau der Kohlenstoffverbindungen," 13. A partial list of places Frey-Wyssling in which reproduced Seifriz's diagram in the 1930s alone (along with an unsubtle hint that Meyer took it without attribution in 1930) includes: Albert Frey-Wyssling, "Der Aufbau der pflanzlichen Zellwände," *Protoplasma* 25, no. 1 (December 1936): 261–300; Albert Frey-Wyssling, "Die Micellarlehre erläutert am Beispiel des Faserfeinbaues," *Kolloid-Zeitschrift* 85, no. 2/3 (1938): 148–58; Albert Frey-Wyssling, *Submikroskopische Morphologie des Protoplasmas* (1938); Albert Frey-Wyssling, "The Submicroscopic Structure of Cell Walls," *Science Progress* 34, no. 134 (1939): 249–62.

was dissatisfied the fact that Staudinger (who used viscometric methods) was producing measurements for the length of cellulose chain molecules that were different by over an order of magnitude from the measurements made by Meyer, Mark, and other x-ray crystallographers.[97] Surely, thought Frey-Wyssling, some middle ground might exist.

Frey-Wyssling developed his new "reticular system" theory seeking to explain optical anisotropy, while also making room for this diversity of cellulose chain measurements. Methodologically, the reticular system model now focused on exploring the intermicellar spaces, rather than the micelles themselves. By examining the intermicellar spaces, Frey-Wyssling reinterpreted the rest of the micellar system as a continuous network of cellulose fibers, with the "micelles" being only the more crystalline *regions* of the reticular system (Figure 4.12).[98] In order to locate and "see" those crystalline regions of the cell wall, Frey-Wyssling deployed his old technique of "staining" and measuring the intermicellar gaps by filling them with gold or silver particles (Figure 4.13). Now, the procedure for polarized light microscopy was the reverse of what he and Ambronn had been doing for forty years: stain the intermicellar space with heavy metals, then use the imbibition method to make the *cell wall* disappear, leaving only the heavy metals behind as the only objects visible under the polarized light microscope.

By modifying the theory of individual crystalline micelles and positing a larger system of parallel cellulose chains to explain the optical phenomena, Frey-Wyssling was now, finally, displacing the micelle as the basic unit whose arrangement caused double refraction in plant matter. Whereas a decade earlier he had started his argument for the micellar theory by discussing the birefringence of whole fibers, in his 1936 essay describing his new reticular theory of cell wall structure Frey-Wyssling started where the x-ray crystallographers started: the atomic structure of molecular cellulose, and the

97. Albert Frey-Wyssling, "Der Aufbau der pflanzlichen Zellwände," 268.

98. *ibid.*

chain structure of fibers composed of repeating units of the same cellulose molecules (Figure 4.10). Micelles were now no longer individual, birefringent crystallites that responded to mechanical forces by realigning: they were about to become an historical footnote.

In Frey-Wyssling's grand synthesis in 1938, *The Sub-Microscopic Morphology of the Protoplasm and its Derivatives*, micelles held an ambiguous ontological status, a reflection of his cell wall models from 1936: micelles were no longer objects or units of matter, but a scale of material organization. Frey-Wyssling's own work with x-ray crystallography had shown him that it was now possible to think of micellar structures as *resolving* down to a molecular, even atomic scales. Seifriz's model from 1929 of cellulose molecules residing inside brick-like micelles may have been entirely hypothetical, but it was constructed based on this increasingly plausible theoretical synthesis that other biologists were beginning to recognize as well.

In 1938, what was supposed to tie together Frey-Wyssling's scales of analysis, from the amicroscopic to the cellular realm, was the "principle of repetition," an idea suggested to him by Meyer and Seifriz's schematic diagrams of cellulose structure. The principle of repetition was, in some sense, a way of translating polymerization from a chemical-molecular process into a useful way of thinking about biological structure; it reflected the growing importance of polymerization in organic chemistry, even if the organic chemists *still* did not agree on how large a chain molecule could be. A corresponding "principle of specificity" was meant to account for the diversity of such measurements, and translate this into a diversity of biological structures:

> There are two guiding principles, of the utmost importance to biomorphology, which are already recognizable in the configuration of chain molecules. They are: 1. The principle of repetition, which is the foundation of all lattice structures and of every form of banding, and 2. The principle of specificity. The first principle is represented, on the one hand, by the ever-recurring members of the chain (intramolecular spacing) and, on the other, by the assemblage into a lattice pattern of kindred chains (intermolecular spacing), as for example frame substances, reserve substances, and lipid layers. Only if all the members of a certain kind of chain are of exactly the same structure can true intermolecular repetition take place. This law does not normally apply to polypeptide chains, since

> their side groups are often of different structure. In consequence, we find the second principle holding sway, *i.e.*, the capacity of otherwise similar molecular elementary units to assume a specific arrangement which may be repeated for its part in long-range periods.[99]

The principles of repetition and specificity were, admittedly, sops to profundity at the conclusion of a drily technical, yet impressive monograph: Frey-Wyssling would occasionally invoke the principle of repetition (and not the principle of specificity) in his later writings, but never with any strong conviction. What *Sub-Microscopic Morphology* held onto with much greater conviction was the old, Nägelian vocabulary because Frey-Wyssling and every other scientist working on fine structure retained polarized light microscopy as a fundamental technique — either as an aid or an alternative to x-ray crystallography.

e. Conclusion: polarized light microscopy and early electron microscopy

By itself, polarized light microscopy shows very little more than an ordinary light microscope; in fact, it often showed far less, since the two Nicols prisms required the use of low-magnification lenses, and they made the optical projection considerably darker. Without the work of Nägeli, Ambronn, Frey-Wyssling, and others on the theoretical underpinnings of polarized light microscopy, it would not have become a useful tool for studying the micellar, and later molecular, architecture of living and non-living matter. Polarized light microscopy could have become useful to biologists without Nägeli, Ambronn, or Frey-Wyssling's theoretical work: the presence and absence of birefringence could have been tied exclusively to the presence of mechanical stress, *à la* von Ebner, or the sign of birefringence could have been used as one of many ways of identifying and classifying organisms and tissues, as von Mohl and Ehrenberg had done. There was nothing about polarized

99. Albert Frey-Wyssling, *Submikroskopische Morphologie des Protoplasmas* (1938), 287; translation from Albert Frey-Wyssling, *Submicroscopic Morphology of Protoplasm*, trans. Mary Hollander, 2nd English ed. (Amsterdam: Elsevier, 1953), 372.

light microscopy that compelled biologists to seek out a molecular and discontinuous approach to living matter. But Ambronn was remarkably consistent, even uncompromising, in his belief in micelles, and polarized light microscopy became the only way to pursue that theory of matter.

What this chapter has shown, however, was that Ambronn could only make a stronger case for the existence and universality of micelles and micellar structures by working through other disciplinary communities. Ambronn's (and later Frey-Wyssling's) work in scientific microscopy and colloid chemistry proved especially important: these were both "disciplines" in relatively loose sense, by the 1910s possessed of official institutions, journals, titles, and informal organizations. Yet they were also technical orientations, communities of common interest centered around the development of either specific tools (polarization microscopy) or topics (aggregates of heterogenous materials) that had wide traction in many other disciplines. Colloid chemistry was, by the 1910s and '20s, the most self-awaredly catholic, interdisciplinary "discipline" devoted to both a wide range of techniques and materials; in 1926 it was both the most convenient and the most appropriate home for the publication of the *Festschrift* for Ambronn's seventieth birthday. The two figures at the center of this chapter, Ambronn and Frey-Wyssling, found ways of navigating colloid chemistry, scientific microscopy, and botany, both by theorizing about what the polarized light microscope was capable of, and by continuing to refine and elaborate the micellar theory. Working in the 1920s and '30s, Frey-Wyssling also had to find ways of technically and theoretically reconciling x-ray crystallography with polarized light microscopy, as these communities struggled to do the same. Each devoted their intellectual and technical resources to visually disaggregating complex colloids into their constituent parts; this chapter has shown just how challenging this endeavor was, and how many different perspectives were required to make it happen.

In 1915 Wolfgang Ostwald began to use the phrase, "the world of neglected dimensions" (*"die Welt der vernachlässigten Dimensionen"*) as an evocative way of explaining the domain of colloid chemistry, a range of scales between pure chemical molecules and visible mechanical phenomena. It was a sentiment that lay behind Frey-Wyssling's table explaining the domains of morphology (Figure 4.6), and he made the connection between his conception of sub-microscopic morphology and Ostwald's vision of colloid chemistry explicit in his rectoral address at the ETH Zürich on November 16, 1957.[100] This line about a "world of neglected dimensions" has been used by historians of science as well, notably by Robert Olby and Lily Kay, to elaborate on the canonical history of molecular biology as an elaboration of macromolecular theory.[101] Olby in particular has characterized the period from the 1910s through the 1940s as one where biologists, physicists, and chemists alike were all trying to understand scales of structure "between the ultramicroscopic and the molecular" by bringing new instruments to bear — arguing that this period cannot be understood as a "conflict of [research] programs and the victory of one over the other with the help of a third."[102] At the same time, however, Olby has also characterized the resolution of the world of neglected dimensions as a result of an "urge to fill the gaps of measurement," by which he means the measurement of high molecular weight molecules leading up to Watson and Crick's information paradigm of the 1950s.[103]

But is the image of a single, long-chain macromolecule (Figure 4.14) a sufficient cognitive foundation to build up an idea of a complex biological structure of, for example, a cell wall or a plant

100. Albert Frey-Wyssling, *Die Welt der vernachlässigten Dimensionen in der Biologie* Eidgenössische Technische Hochschule Kultur- und Staatswissenschaftliche Schriften, Heft 102 (Zürich: Polygraphischer Verlag, 1958).

101. Robert C. Olby, "Structural and Dynamical Explanations in the World of Neglected Dimensions," in *A History of Embryology*, ed. T. J. Horder, J. A. Witkowski, and C. C. Wylie (Cambridge: Cambridge University Press, 1986), 275–308; Robert C. Olby, "The Significance of the Macromolecules in the Historiography of Molecular Biology," *History and Philosophy of the Life Sciences* 1, no. 2 (1979): 185–98; and Lily E. Kay, "Molecular Biology and Pauling's Immunochemistry: A Neglected Dimension," *History and Philosophy of the Life Sciences* 11, no. 2 (1989): 211–19.

102. Robert C. Olby, "Structural and Dynamical Explanations in the World of Neglected Dimensions," 302.

103. Robert C. Olby, "The Significance of the Macromolecules in the Historiography of Molecular Biology," 197–98.

fiber? Given that such atomic-molecular diagrams were readily available by 1933, and that Frey-Wyssling continued research on the fine structure of cell walls well into the 1960s: probably not. The difficulty remains in how such molecules are arranged into the larger biological whole — an argument long made by some geneticists, who have pointed to the interplay between DNA code and the molecular-morphological configuration of chromosomes and the nucleus. In contrast, both micellar theory and colloid theory were often intended to connect larger- and smaller-scale theories of matter and material hierarchies. In molecular genetics, a partial strand of DNA has achieved an iconic status, a symbol of the physicalist and informational approaches that hold molecular genetics together as a discipline.[104] Sub-microscopic morphology, however, seems to have required a whole, very dense book like Frey-Wyssling's *The Submicroscopic Morphology of the Protoplasm and its Derivatives.*

After the 1940s, the only area of physical chemistry that retained micelles as a supra-molecular unit of structure was soap and detergent chemistry, which had become a particularly robust corner of colloid chemistry.[105] In his third, 1953 edition of *Submicroscopic Morphology*, Frey-Wyssling revised his table (Figure 4.15) of the realms of morphology, its fourth row suffering the most dramatic changes. It now connected: "Fine-structure, micellar studies, electron microscope, colloid dimensions, > 1mμ."[106] All but one of the levels on Frey-Wyssling's table in 1953 are arguably tied to real things, and all but one level of the morphological hierarchy has an obvious ontological foundation. Organs, tissues, cells, molecules, and atoms are recognizably real, but "Fine-structure" is slipperier, tied more to its method of investigation than any clear unit or object. As biologists

104. See note 13 of the Introduction.

105. Brian Vincent, "McBain and the Centenary of the Micelle," *Advances in Colloid and Interface Science* 203 (January 2014): 51–54.

106. Albert Frey-Wyssling, *Submicroscopic Morphology of Protoplasm*, trans. Mary Hollander, 2nd English ed., 6.

rejected colloids and micelles as theories of matter, Frey-Wyssling's table was left with a major conceptual gap between the cellular and molecular scales of morphological research.[107]

In the postwar era, Frey-Wyssling dropped his drawn micellar diagrams in favor of electron micrographs, and electron microscopy more fully stepped in to fill the conceptual gap left in Frey-Wyssling's hierarchy of morphology; despite the fact that micelles are not the same kind of thing as electron micrographs, they seem to have occupied the same intellectual domain, and the latter came to replace the former. Frey-Wyssling was one of the earliest European biologists to adopt the electron microscope, obtaining one as early as 1944.[108] Whereas polarized light microscopy requires a great deal of interpretive and inferential skill, electron micrographs offer direct images of fine structure, once the difficulties in specimen preparation are overcome. When they could be made, these direct images quickly replaced the micellar diagrams that had proliferated in Frey-Wyssling's articles and books through the 1940s. No longer needed were theoretical entities like micelles to explain difficult-to-understand optical phenomena, with the proof of fine structure suspended somewhere in between an empirical observation and a theory of matter; no longer needed was an elaborate optical theory explaining how colloidal particles and the colloidal medium interacted. Even a principle of molecular repetition was not needed if one could simply look at and measure the dense mat of cellulose fibers under incredible magnification:

> Micrographs of shadow casts of primary cell membranes executed by my assistant [Kurt] Mühlethaler in the laboratory of [Ralph] Wyckoff confirm what the indirect methods had predicted about the submicroscopic wall texture: there are microfibrils with a diameter of 200-250 Å, forming a crossed system…with the majority lying in the transverse direction. New facts are that these microfibrils are sharply defined and that they seem to be partly interwoven as in a textile fabric.[109]

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107. See also Robert C. Olby, "Structural and Dynamical Explanations in the World of Neglected Dimensions," 300.

108. Albert Frey-Wyssling and Kurt Mühlethaler, "Elektronenoptische Abbildung des submikroskopischen Gel-Feinbaues," *Vierteljahrsschrift der naturforschenden Gesellschaft in Zürich* 89 (1944): 214–15; on Frey-Wyssling and Mühlethaler's acquisition and promotion of the electron microscope in European molecular biology, see Bruno Strasser, *La fabrique d'une nouvelle science la biologie moléculaire à l'âge atomique (1945-1964)* (Firenze: Leo S. Olschki, 2006).

109. Albert Frey-Wyssling, "The Growth in Surface of the Plant Cell Wall," *Growth* 12, supp. (1948): 151–70.

Facts like definition or diameter in an electron micrograph are quite immediate (Figure 4.16): no "principle of repetition" or speculative mechanical theory is needed to gain this kind of structural knowledge. Or, at least, the principle of repetition was not needed if and only if the scientist was satisfied with such of images of fine structure like those in Figure 4.16: the earliest electron micrographs did not actually achieve levels of magnification or resolution for biological materials that allowed for direct observation of molecule-scale structures.

Nicholas Rasmussen has argued that early electron microscopy was a fairly conservative endeavor, given the novelty of the instrument and the difficult preparation techniques it required.[110] Crucially, polarized light microscopy could be used on *living* specimens, while early electron microscopes required the specimen to sit in a vacuum, before being vaporized just as the electron beam made the image. Thus, polarization microscopy and diagramming practices continued to be used to check preparation and imaging techniques, setting up expectations before seeing an electron micrograph as either an accurate or distorted image of biological structure.[111] From the 1930s through the early 1950s electron micrographs would often be viewed as part of a larger system of images that included diagrams describing micellar, molecular, and atomic structure.

When polarized light microscopy, ultramicroscopy, x-ray diffraction, and other indirect tools were the only methods to "see" submicroscopic structure, the diagram was not just an interpretive tool: the diagram was the argument. As electron microscopists grew more confident and the quality and reliability of electron micrographs improved, micellar and molecular diagrams became less important: with a good direct image from the electron microscope, the microgram could be

110. Nicolas Rasmussen, *Picture Control: The Electron Microscope and the Transformation of Biology in America, 1940-1960* (Stanford: Stanford University Press, 1997).

111. Francis O. Schmitt, "Electron Microscopy in Morphology and Molecular Biology," in *Vierter internationaler Kongress für Elektronenmikroskopie, Berlin 10.–17. September 1958*, ed. W. Bargmann et al., vol. 2 (Berlin: Springer-Verlag, 1960), 1–16.

sufficient proof, and diagrams were only secondary heuristic aids. Diagrams and schematic drawing were no longer *necessary* to mediate between theories of matter and biological structure, but merely aids. For a specialist working in cell structural biology, this is no loss at all. For a biologist or lay person working at much higher or much lower levels in the hierarchy, however, the absence of an ontological, structural unit *might* explain why organismal experience seems so alien from the perspective of modern molecular biochemistry, and vice versa.

Chapter 5: The Building Blocks of the Biological Microworld, 1924–1941

How did Wilhelm Josef Schmidt (1884–1974) begin to see "the organization of the cell's molecular order" in 1939 (Figure A)?[1] As mentioned in the beginning of the introduction, Schmidt's 1939 lecture, "*Der molekulare Bau der Zelle*" presented the first ever schematic image of the cell protoplasm as an argument for why biologists had been unable to conclusively find the fine structure of protoplasm. If protoplasm's fine structure were genuinely "wild" and disordered, then the ordinary light microscope would never be able to reveal it.[2] This was an image that could have only arisen from Schmidt's imagination, drawing from the molecular imagery that had been proliferating across the physical and biological sciences in the 1920s and '30s. This image shows us historically that by 1939, a new form of biological reasoning had come into its own, and that materialist and reductionist approaches to histological, cellular, and sub-cellular organization could now be molecular.

This chapter will show how Schmidt in 1939 was able to make invisible molecules in the "optically empty" protoplasm visible and comprehensible on paper and on stage. Schmidt's argument for the reality of fine molecular structure arrived largely through a schematic, graphical iconography: the protein chains by means of analogy and borrowing from fiber chemistry, the lipid bilayer from a ball-and-stick image that originated as a heuristic analogy or conceptual aid for the abstract physical concept of *molecular orientation*. Schmidt's exploration of fiber and cytoskeleton structure had more

1. W. J. Schmidt, "Der molekulare Bau der Zelle," *Nova Acta Leopoldina* 7 (1939): 1–24, on 7.
2. *ibid.,* 12, 15–16.

bearing on theories of protoplasmic structure than the lipid structures in this image. Yet his graphical representation of molecular orientation is historically much more important for what it shows about the state of molecular theory. The most expressive and most interesting parts of the 1939 image are the three, globular, fatty structures. It is these three structures that speak most to the historical development of the biological microworld. The vacuole (upper-right), liposome (lower-right), and triglyceride droplet (middle-left) are each composed of individual molecules that have gained highly regular structure. Within the triglyceride droplet the molecules are arranged at random, but at the surface the individual triglyceride molecules are all oriented facing inward. The vacuole and liposome are even more striking, with the individual lipid molecules forming orderly bilayers to contain innumerable water molecules between the lipids' heads; meanwhile, a few individual lipid molecules float freely in the rest of the protoplasm. Taken together — and along with the other diagrams Schmidt used in his 1939 address — these individual lipid molecules are understood to have their own ability to move, orient, and arrange themselves. The ball-and-stick image that was eventually used to represent lipid lamellar structures in living cells was not just a schematized representation of a chemical formula: it allowed biologists to imagine that living matter was composed of molecules of definite size, shape, and orientation, and that those molecules could construct a complex, living cell strictly by sorting, aggregating, and segregating themselves through physical forces. In other words, biologists in the mid-1930s were developing an essential part of a biological microworld not necessarily through mathematical physics or a deep understanding of structural chemistry, but by understanding a diagrammatic convention as a realistic representation of molecular reality.

Recent work in the history of physics and the history of chemistry has stressed the roles of imagination and visual culture in constructing theories of the microworld of sub-microscopic atoms,

molecules, and otherwise invisible particles and forces.[3] Ursula Klein and David Kaiser have each argued that "paper tools," mathematical symbols, diagrams, and even doodles can play a crucial role in directing and keeping account of unruly and abstract scientific thought.[4] And building upon the work of Klein and Kaiser, Alan Rocke has recently written about the role of imagination in the sciences of atoms, molecules, and forces that are fundamentally beyond the reach of human senses. Rocke argues that mental images were essential in turning organic chemical work with flasks and analytical balances into an entire metaphysics of molecular structures. The psychic and mental lives of scientists work in large part through symbols and images, and Rocke, Klein, and Kaiser alike argue that paper tools and diagrams can be thought of as a pale shadow of scientists' dreams and flights of fancy of the microworld — dreams and images that are often not condoned in "proper" scientific settings like scholarly journals or monographs. This chapter takes a more limited approach to these imaginings and images of the microworld, if only because a full exploration into the inner psychic lives of long-dead and ill-recorded scientists is frighteningly difficult, as Rocke himself has admitted. This chapter will look most carefully at the more didactic genres of physical-chemical writing and image-making, because diagrams and invocations of imagination or visual analogy are often used to communicate difficult theories to audiences of varying degrees of impressionability.[5] This genre of scientific writing carries the weight of intentional transmission and translation, and such images and

3. Alan J. Rocke, *Image and Reality: Kekulé, Kopp, and the Scientific Imagination*, (Chicago: The University of Chicago Press, 2010).

4. Alan Rocke explicitly cites Klein and Kaiser's work as essential in his conception of scientific imagination, though he also is clear that he is trying to put material images (e.g., doodles and formulae on paper) against a larger setting of the psychic aspects of scientific thought. Ursula Klein, *Experiments, Models, Paper Tools: Cultures of Organic Chemistry in the Nineteenth Century* (Stanford: Stanford University Press, 2003); David Kaiser, *Drawing Theories Apart: The Dispersion of Feynman Diagrams in Postwar Physics* (Chicago: University of Chicago Press, 2005).

5. This is somewhat in contrast to the also-growing literature on models and modeling, the enthusiasm for which has been met by historians with increasing caution as many have noticed slippage between actors and analysts' use of the words "model" and "modeling." For example, in Angela N. H. Creager, Elizabeth Lunbeck, and M. Norton Wise, eds., *Science Without Laws: Model Systems, Cases, Exemplary Narratives*, (Durham: Duke University Press, 2007), the contributors by and large recognize that models and modeling look quite different in various disciplines, while many of the contributors in the earlier volume Soraya de Chadarevian and Nick Hopwood, eds., *Models: The Third Dimension of Science* (Stanford, Calif: Stanford University Press, 2004) focused on models were three-dimensional material objects.

analogies are among the more potent and portable elements of the genre. Even Aristotle in *De Anima* identified the human imagination's capacity for creative image-making beyond common perception, as a place for invention and free association, and as a heuristic guide to both the senses and to reason. Situated between different kinds and degrees of mastery of abstract physical theories, the imagination is a place where heuristic guides and assumptions about reality can slip — and this slippage between nominalist and realist representations of the microworld became easier in the tricky transmission and translation of difficult theories across disciplines.

Whereas the previous chapter focused largely on the technical and theoretical issues surrounding polarized light microscopy, this present chapter will show how Schmidt learned, absorbed, and translated molecular theory through graphical convention and visual imagination, and not by difficult physics or clever experiments. Many of the individual, iconographic elements of Schmidt's 1939 molecular schematic diagram of the protoplasm existed before, including the ball-and-stick image of the lipid; Schmidt's particular skill was at interpreting observations under polarized light through these images, making arguments in scientific journals based in part on molecular diagrams. Where Hermann Ambronn and Albert Frey-Wyssling labored in the interwar period to make sub-microscopic morphology technologically possible, Schmidt made molecular theory more relevant and more accessible to the broader concerns of biology by visually showing how invisible molecules could come together to form larger structures.

This chapter will proceed along two major lines, reflecting the two structural principles expressed in Schmidt's 1939 molecular image of the protoplasm: protein chain molecules, and the lipid bilayer lamellae. The first section discusses Schmidt's articulation of his conviction that animal bodies were composed micellar building blocks, or *Bausteine*. This approach offered Schmidt a productive way to use polarized light microscopy to study a wide range of animal tissues. By the

mid-1930s Ambronn's micellar theory began to reveal its limitations, and Schmidt began to explore recent ideas of atomic and molecular structure for new ways to interpret the interference patterns visible in the polarized light microscope.

The bulk of this chapter is a history of this image of the individual lipid molecule, the image of the lipid bilayer, and the science of how lipids molecules can arrange *themselves* into vacuole, liposome, and, crucially, cell membrane structures. Starting with the history of attempts to measure the diameter of oil molecules at the end of the nineteenth century, middle four sections will tell the history of the discovery of molecular dimensions and, most crucially, molecular orientation. The theory of molecular orientation came out of attempts to understand surface tension, and the attempt to reconceptualize colloidal structure in terms of surface phenomena and surface energy. The concept of molecular orientation emerged from physical chemistry in the 1910s and transformed from a relatively difficult synthesis of mathematical models and abstract physical theories to an easily manipulated image or icon, on paper and in the imagination. Its most famous early use was in 1935 by James F. Danielli (1911-1984), who suggested that the lipid bilayer structure was an essential feature of cell membrane structure (Figure 5.1).[6] At least later in life Danielli stressed that the lipid bilayer was not his idea; he argued, without a hint of doubt, that the lipid-bilayer "would have been obvious to any competent physical chemist," and that such an idea "flowed almost automatically" from the basic physical chemistry of the 1930s.[7] Yet while there are histories of the cell membrane,

6. James F. Danielli and Hugh Davson, "A Contribution to the Theory of Permeability of Thin Films," *Journal of Cellular and Comparative Physiology* 5, no. 4 (1935): 495–508.

7. James F. Danielli, "The Bilayer Hypothesis of Membrane Structure," *Hospital Practice* 8, no. 1 (1973): 63-71. Danielli here notes that in 1935 he was not aware of Evert Gorter and François Grendel's 1925 paper, "On Bimolecular Layers of Lipoids on the Chromocytes of the Blood" — now popularly viewed as the first discovery of a lipid bilayer — despite the fact that Gorter was a well known expert on surface physical chemistry working in British circles. Although a more thorough citation analysis needs to be performed, it appears that Gorter and Grendel were not known for their membrane hypothesis until the late-1930s, by which time the idea of a lipid bilayer also had an established graphical representation, as the rest of this chapter will show. Evert Gorter and Francois Grendel, "On Bimolecular Layers of Lipoids on the Chromocytes of the Blood," *The Journal of Experimental Medicine* 41, no. 4 (1925): 439–43.

there are no histories of the lipid bilayer itself, much less of the history of the graphical representation of this now-ubiquitous, "obvious" essential structure.[8]

*a. W. J. Schmidt and the "*Bausteine*" of animal bodies*

Like Ambronn, Schmidt also called himself an *"Einsamer"* in his personal recollections, but, unlike Ambronn, one is inclined to take Schmidt at his word. One of his friends remembered that "from time immemorial he was a researcher of silence, and he spent every possible moment in his laboratory — and that was true for Sundays and even the high Christmas season."[9] Yet Schmidt was also fondly remembered as a genuinely enthusiastic colleague and educator, and he was unusually honored with three separate *Festschriften* and scholarly birthday celebrations for his sixtieth, seventieth, and even eightieth birthdays; he died one week short of his ninetieth birthday, foreclosing the possibility of a fourth. Comparing himself to his botanical counterpart Frey-Wyssling, Schmidt wrote that the Swiss scientist had the fantastic "luck" to have such skilled mentors and teachers in physics and chemistry, he struggled to learn those topics by himself.[10] Frey-Wyssling for his part remembered that only four of Schmidt's 404 scientific publications were co-authored, and that his "inflexible will to observe everything personally and to interpret and edit his findings alone was part of his special intellectual constitution."[11]

Schmidt's individualism was a product of his training in comparative anatomy at the rather old-fashioned zoological institute in his home city of Bonn, where he completed his graduate

8. See, for example, Jonathan Lombard, "Once upon a Time the Cell Membranes: 175 Years of Cell Boundary Research," *Biology Direct* 9, no. 32 (2014).

9. J. Grehn, "Zum Tode von Wilhelm J. Schmidt (21.2.1884 - 14.2.1974)," *Microscopica Acta* 76, no. 1 (1974): 1–8, on 5.

10. W. J. Schmidt, "Aus meiner Werkstatt," *Bericht der oberhessischen Gesellschaft für Natur- und Heilkunde zu Gießen, neue Folge, naturwissenschaftliche Abteilung* 33, no. 4 (1964): 217–37, on 224.

11. Albert Frey-Wyssling, "The Scientific Work of W. J. Schmidt," *Microscopica Acta* 77, no. 2 (July 1975): 105–13.

education in 1908, and where he worked as an extraordinary professor until 1926. He was originally passionate about studying reptiles, and his first publications before and during the First World War were comparative studies of gecko skin, muscle, and integument. Schmidt soon acquired a love of the seashore, after winning several state and university stipends to work at the marine biological stations in Helgoland, Corscia, Naples, and the Russian-operated station at Villefranche. Schmidt likely picked up polarization microscopy at Naples in the 1910s, in order to study the structure of oyster shells and mother of pearl — and it was at Villefranche that Schmidt met the Armenian-born, Swiss-trained physician Wadui Pogossjanz, whom he married in 1912. According to his autobiographical remarks in 1964, Schmidt's initial excitement about polarized light microscopy led him to Victor von Ebner's 1882 monograph on the causes of optical anisotropy, which in turn led him to consider Ambronn's theories and methods soon after the First World War.[12]

Schmidt's enthusiasm for polarized light microscopy and for Ambronn's theory and methods led him to revisit his earlier work on reptiles and mollusks, examining them now under the polarized light microscope. The resulting 500-page comparative study, *Die Bausteine des Tierkörpers in polarisiertem Licht* (*The Building Blocks of the Animal Body in Polarized Light*) was a combination of nineteenth century-style comparative anatomy writing and a very loose application of Ambronn's imbibition method and micellar theory. For Schmidt the term "building block," or *Baustein,* had something of a double meaning. On the one hand, the building blocks of animal bodies included materials that were not cells:

> I have chosen the expression "building block" (*Bausteine*) and not the word "tissue" (*Gewebe,* alt. "fabric"), because by the latter term one only thinks of examining cells, and because between crossed Nicols one can examine not only these, but also the production of intercellular and cuticular substances, and many considerable parts of the body are not even cellular.[13] (See Appendix A for the term "crossed Nicols.")

12. W. J. Schmidt, "Aus meiner Werkstatt," 223.
13. W. J. Schmidt, *Die Bausteine des Tierkörpers in polarisiertem Lichte* (Bonn: F. Cohen, 1924), iv–v.

The other meaning of "building block," however, tied animal bodies to polarized light microscopy and Ambronn's micellar theory. The building blocks that Schmidt spoke of were the ones that could be seen under polarized light, the crystalline micelles; he was not concerned with the more fluid parts of the body. Most of *Die Bausteine* was devoted to the "skeletal" structures of protists, invertebrates, and vertebrates alike — shells, scales, bones, hair, and teeth. One short section dealt with muscle (or muscle-like structures in lower organisms), and an even shorter section covered solid and fatty excrescences. This was low-hanging fruit: most of the tissues Schmidt examined were hard structures, and determining their patterns and signs of birefringence could be done quickly between crossed Nichols, and did not require Ambronn's imbibition method. This was also the first comparative anatomical work with polarized light since 1861, and Schmidt was rather familiar with the organisms already. The 230 micrographs in *Die Bausteine* were made at relatively low magnifications, typically below 100:1, and were accompanied by simple descriptions of which areas were birefringent or could be made birefringent. This was not the kind of micelle-by-micelle, fine structural work that Frey would start doing in the late-1920s. *Die Bausteine*'s style of anatomy was at the scale of tissue structure, devoted to examining what was and was not birefringent, and only occasionally using Ambronn's imbibition method to highlight the existence of birefringence.

The rhetorical power of *Die Bausteine*, however, was fairly significant: by starting with diatom shells, bone, and teeth, and then to hair, muscle, and nerve, Schmidt demonstrated that polarized light microscopy was useful in studying bones and shells, but might later become equally useful in studying fibrous structures like cartilage and muscle, and then even truly soft structures like nerves. The micellar theory, Schmidt argued,

> illuminates the existence of a continuous sequence of steps of building blocks, from the atomic up to the histological structures, and together reveal that the structure-giving forces within this range generally remain the same: histological structures are also caused by a kind of crystallization process, by micellar-crystallization (*Micellarkristallisation*).[14]

Schmidt's enthusiasm for polarized light microscopy was also nearly boundless, and in the conclusion to *Die Bausteine* Schmidt rather breathlessly promoted the technique as a crucial new resource for everything from developmental biology to pathology:

> Between crossed Nicols is the most convenient way to examine the formation and degeneration of birefringent parts, the *occurrence of crystalline products* in cells (*e.g.,* guanine), the first appearance of calcium carbonate skeletons (*e.g.* in echinoderm larvae), the development and degeneration of nerve cords, the conversion of striated muscle *into electric organs* and the progressive *hardening of enamel*.[15]

Yet in focusing on the essentially crystalline nature of all of these structures, Schmidt also suggested that this kind of study was essentially different from the methods being promoted by the more colloidally-inclined biologists — as he put it, the one "enriches" the other.[16] If polarized light microscopy was good for detecting anisotropy in crystalline bodies (*i.e.* the micelles), then everything from shells to muscle fiber had to be at least somewhat crystalline, or at least "half-isotropic" micellar complexes.

The success of *Die Bausteine des Tierkörpers* had a similar effect on Schmidt's life and career as Ambronn's 1890s research had had on the latter scholar. In January 1923 Schmidt became one of the editors of the *Zeitschrift für wissenschaftliche Mikroskopie und mikroskopische Technik*, where he became known as an expert in the polarized light microscopy of cell, chromosome, and mitotic spindle structure. And just as Ambronn's work had brought him into Zeiss, *Die Bausteine* allowed Schmidt to establish what would become a long-standing relationship with the Ernst Leitz optical firm in Wetzlar, one of Zeiss' strongest competitors in the microscope market even today. From the beginning *Die Bausteine des Tierkörpers* was written with the explicit material and financial support of

14. *ibid.,* 498, several emphases removed.

15. *ibid.,* 504.

16. *ibid.,* 503.

Leitz, which also paid the printing costs of the 230 micrographs. Schmidt initially used a large, complicated Leitz model CM petrographic microscope, which was built for quantitative measurement of birefringence at low magnifications — hence the low-magnification images in *Die Bausteine*. The success of Schmidt's monograph and his growing relationship with the company led to Letiz's development and sale of the CBMP microscope in 1925, the first polarized light microscope built specifically for biological research at higher magnifications.[17] And in 1926, with Leitz's support, Schmidt was hired by the University of Giessen, located a short 16 km away from Wetzlar.

Schmidt's scientific style also shows some of the diversity within scientific microscopy: Schmidt's practice and expositions on polarized light microscopy focused largely on qualitative concerns, especially on simply making birefringence visible in biological specimens at all. Schmidt wanted to use polarized light microscopy to examine cellular, extra-cellular, and tissue-scale objects, in contrast to Frey-Wyssling's dive deeper and deeper into one sub-cellular structure, the cell wall and cellulose structure. Ambronn and his colleagues at Zeiss and Jena had been quite concerned with theories of matter, the quantified measurement of birefringence values, diffraction of different wavelengths of light, particle size, etc., all showing their closer scientific connections to concerns within physics and physical chemistry. Schmidt, the product of a classical training in comparative anatomy and recently selected to head Giessen's anatomy institute, did not care for such issues in physics.

17. W. J. Schmidt, "CBMP von E. Leitz, Wetzlar, ein Polarisationsmikroskop für Biologen," *Zeitschrift für wissenschaftliche Mikroskopie und mikroskopische Technik* 42, no. 3 (1925): 313–21. Besides being designed around higher-power objectives, the CBMP also used a simpler Glan-Thompson polarizing prism, rather than the Ahrens-type prisms used for petrography. The Ahrens prism could transmit a beam with a higher degree of polarization, allowing for more precise quantification of birefringence, but its three-part construction left a visible seam in the middle, making observation of finer structures impossible.

Between 1924 and 1942 Schmidt wrote no fewer than eleven lengthy treatises on polarization-optical methods alone.[18] While a few of these longer methodological treatises addressed methods for determining exact birefringence values, Schmidt's primary concern was to isolate different parts of cellular structure, and make them visible — on paper and under the microscope — by finding the sign of birefringence in each part. In doing this he was beginning to move beyond the version of the Wiener mixed-body theory that Ambronn and Frey had generated, instead using the micellar diagrams themselves to work out how different shapes of micellar particles might produce different optical effects: the idealized "platelets" and "rodlets" were giving way to more realistic and more diverse suggestions of microphysical structure (Figures 5.2 and 5.3).

One of Schmidt's most difficult technical accomplishments in this regard was his study of the frog eye retina in 1935.[19] This was part of his larger turn toward studying the fine structure of soft cells with few obviously-crystalline parts. Not only are there no obviously crystalline structures in rod cells, but the whole retina cell is a confusing tangle of fatty and proteinaceous parts: the challenge was to find ways of manipulating the cells to get these different kinds of parts to look visibly different

18. In addition to *Die Bausteine Des Tierkörpers in Polarisiertem Lichte* in 1924, these were: W. J. Schmidt, "Bestimmung der Lage der optischen Achse in Biokristallen," in *Abderhaldens Handbuch der biologischen Arbeitsmethoden*, Abt. V, Teil 2/II (Berlin: Urban & Schwarzenberg, 1929), 1357–1400; W. J. Schmidt, "Dichroitische Färbung tierischer und pflanzlicher Gewebe," in *Abderhaldens Handbuch der biologischen Arbeitsmethoden*, Abt. V, Teil 2/II (Berlin: Urban & Schwarzenberg, 1931), 1835–1924; W. J. Schmidt, "Polarisationsoptische Analyse des submikroskopischen Baues von Zellen und Geweben," in *Abderhaldens Handbuch der biologischen Arbeitsmethoden*, Abt. V, Teil 10/I (Berlin: Urban & Schwarzenberg, 1934), 435–665; W. J. Schmidt, *Die Doppelbrechung von Karyoplasma, Zytoplasma, und Metaplasma*, Protoplasma-Monographien, Bd. 11 (Berlin: Gebrüder Borntraeger, 1937); W. J. Schmidt, "Polarisationsoptische Erforschung des submikroskopischen Baues tierischer Zellen und Gewebe: Der experimentelle Weg und einige Beispiele," (see note 63, below); W. J. Schmidt, "Die Doppelbrechung des Protoplasmas und ihre Bedeutung für die Erforschung seines submikroskopischen Baues," (see note 65, below); W. J. Schmidt, "Neuere polarisationsoptische Arbeiten auf dem Gebiete der Biologie: I. Bericht," *Protoplasma* 29 (1938): 300–312, 435–67; W. J. Schmidt, "Neuere polarisationsoptische Arbeiten auf dem Gebiete der Biologie: II. Bericht" *Protoplasma* 34 (1940): 237–313; W. J. Schmidt, "Neuere polarisationsoptische Arbeiten auf dem Gebiete der Biologie: III. Bericht," *Protoplasma* 37 (1942): 86–153.

A partial bibliography of Schmidt's work before 1945 was published in R.E. Liesegang, "W. J. Schmidt 60 Jahre alt," *Kolloid-Zeitschrift* 106, no. 2 (1944): 135–37.

19. W. J. Schmidt, "Doppelbrechung, Dichroismus, und Feinbau des Aussengliedes der Sehzellen vom Frosch," *Zeitschrift für Zellforschung und mikroskopische Anatomie* 22, no. 4 (1935): 485–522.

under polarized light. This included not only trying out immersion media with different refractive indices, but also various regimes of dehydrating, heating, stretching, and staining. While the retina cell as a whole showed positive birefringence along the long axis of the cell, Schmidt found that this was due in large part to the lipid component; yet, he struggled to work out exactly how the lipid parts were oriented. Still, he found several ways of cancelling out the optical effect of the lipid layers so that he could focus on the even more problematic issue of the arrangement of proteins. Schmidt concluded that, not only were the layers of lipid and protein arranged in alternating platelets, but the proteins themselves seemed to be arranged radially within each platelet, rather than jumbled at random or in a "tangential" or concentric circular pattern (Figure 5.4).

Despite the level of detail he was able to achieve, Schmidt realized that, especially with his description of lipid layers, he was missing a level of fine detail: most of his attempts to discover the intrinsic birefringence of various micellar parts of the retinal cell were frustrated by how many different parts were causing form birefringence. His lengthy concluding remarks spoke more to what his methods were able to accomplish than to any definitive statements of structure, beyond the radial arrangement of proteins in the non-lipoidal parts of the retinal cells. Between 1935 and 1939, Schmidt began to look for a new way to determine and describe a finer level of detail, and a new way to interpret what could be seen under the polarized light microscope. When Schmidt found images of molecular lipid structures, he had also found an entire world of physical and colloid chemistry that had not yet been used to explore biological fine structure.

b. The "molecule" up to 1924

It was impossible to make arguments about the molecular structure of biological matter before the interwar period. The word "molecule" itself was an underdetermined concept in the

nineteenth century despite its common use, and it was only in the years after the First World War that the molecule was clearly conceived as an assemblage of atoms with definite shape. The word "molecule" has its origins in Pierre Gassendi's *Syntagma Philosophicum* (published posthumously in 1658), a speculative work on Epicurean mechanical philosophy, and is thus allied with René Descartes' corpuscular metaphysics; for Gassendi the Latinate neologism *molecule* would simply have meant "little mass."[20] Corpuscular and discontinuous theories of matter had little bearing on biology in the nineteenth century, perhaps due in part to chemists' and physicists' continuing disagreement over the nature of the molecule as well: the physicists' "atom" and "molecule" were nearly incommensurable with those of the chemist, well into the twentieth century.[21] Even if chemists were essentially united in a practical or pragmatic understanding of molecular *identity* by the 1860s — *i.e.,* understanding a molecule as a minimal unit of a distinct chemical species that could be identified by specific molecular weight — then exactly how this could be reconciled with physicists' views of molecular *forces* remained an open question.

Thus on the one hand chemists could disagree over whether atoms and molecules were real, indivisible particles, or if they were merely formulaic conventions on paper alone.[22] On the other hand, physicists' formal mathematical equations left a great deal open to interpretation, and, on paper at least, the physicists' mathematics had little to do with the chemists' increasingly elaborate

20. "Molecule, N.," *OED Online* (Oxford University Press), accessed 9/23/14, http://oed.com/view/Entry/120852.

21. For an overview see Hans-Werner Schütt, "Chemical Atomism and Chemical Classification," in Mary Jo Nye, ed., *The Modern Physical and Mathematical Sciences*, The Cambridge History of Science vol. 5 (Cambridge: Cambridge University Press, 2002), 237-254. To a lesser extent a gap between physical and chemical conceptions of molecules and atoms has persisted through the twentieth century, *e.g.* in approaches quantum molecular structure; see Kōstas Gavroglou and Ana Simões, *Neither Physics nor Chemistry: A History of Quantum Chemistry* (Cambridge: MIT Press, 2012).

22. Much of Mary Jo Nye's scholarly work is devoted to the tangled problems of 1) chemists' and physicists' radically different conceptions of atoms and molecules, and 2) disagreement among physicists about the continuity vs. discontinuity of matter; see for example Mary Jo Nye, *From Chemical Philosophy to Theoretical Chemistry: Dynamics of Matter and Dynamics of Disciplines, 1800-1950* (Berkeley: University of California Press, 1993); or the classic, *Molecular Reality: A Perspective on the Scientific Work of Jean Perrin.* (London: Macdonald, 1972), among many others. Nye has typically focused on the links between discipline and epistemology, leaving room both for biographical studies and for studies of disciplines that fall outside the specific scope of her later monographs; see for example Peter J. Ramberg, *Chemical Structure, Spatial Arrangement: The Early History of Stereochemistry, 1874-1914* (Aldershot: Ashgate, 2003).

written formulas for molecules, reactions, and products. James Clerk Maxwell's physical definition of molecules in thermodynamics and gas law, for example, hypothesized that molecules might alternately be "portions of [a gas] which move about as a single body," or "pure centers of force endowed with inertia, or the capacity of performing work while losing velocity."[23] By the end of the nineteenth century, even as physicists and chemists were knitting together kinetic theory and the behavior of specific chemical substances, physicists found themselves again embroiled in tough metaphysical debates about the continuity or atomicity of matter, tussling over whether thermodynamic equations ontologically privileged either energy, on the one hand, or a statistical understanding of atomic or molecular behavior, on the other.[24] Especially for physiologists with a clear physicalist bent, the absolute primacy of the Second Law of Thermodynamics could suggest that "molecules" were necessarily indeterminate, statistical, wandering beings, rather than clearly defined structural members of a living machine.[25]

Despite the centrality of thermodynamics in physicists' and physicalist physiologists' understanding of the molecule, the physical chemistry of fats played a very different and genuinely outsized role in changing how molecules were conceived. Partly by historical accident, the physical investigation into fats began with physicists' attempts to quantify both surface tension and molecular dimensions. Quite famously, in the early 1880s, while caring for convalescent parents in Braunschweig, Germany, Agnes Pockels (1862-1935) noticed that the surface tension of her dishwater changed dramatically when it became slicked with oil. Using tin from a can of Liebig's

23. James Clerk Maxwell, "On the Dynamical Theory of Gases," *Philosophical Magazine* 4th ser., vol. 35 (1868): 129–45, 185–217; see also Crosbie Smith, *The Science of Energy: A Cultural History of Energy Physics in Victorian Britain* (Chicago: University of Chicago Press, 1998), 244-247.

24. Theodore M. Porter, "The Death of the Object: Fin de Siècle Philosophy of Physics," in *Modernist Impulses in the Human Sciences, 1870-1930*, ed. Dorothy Ross (Baltimore: Johns Hopkins University Press, 1994), 128–51; and Richard Staley, "The Fin de Siècle Thesis," *Berichte Zur Wissenschaftsgeschichte* 31, no. 4 (2008): 311–30.

25. For example, the English cytologist James Gray clearly believed that the determinacy of heredity and development were at odds with the kind of thermodynamic and statistical "molecular systems of which we have so much reliable knowledge." James Gray, *A Text-Book of Experimental Cytology* (Cambridge: The University Press, 1931), 14.

meat extract and her father's pharmaceutical balance (Figure 5.5a), Pockels built the first instrument to quantitatively measure the surface tension of thin liquid films: a broad rectangular trough, the scale measuring how much weight was required to separate a 6mm tin disk from the surface of water contaminated with oil, and degree of contamination adjustable by a long tin or paper strip that scraped the water's surface, stretching or compressing the oil slick.[26]

Meanwhile, in 1889 Lord Rayleigh (John Willaim Strutt, 1842-1919) had begun to investigate the well-known phenomenon of camphor dancing upon water, and the interruption of that dancing by even a minute amount of oil. Using a "sponge bath of extra-size," Rayleigh, likely working with his wife Evelyn Balfour, drew a 33" diameter bath and placed camphor flakes on the surface; then, using a loop of platinum wire, deposited tiny amounts of olive oil, which he claimed to be able to measure down to a twentieth of a milligram.[27] By measuring the amount of olive oil required to stop the camphor from moving, and dividing that volume by the diameter of the tub, Rayleigh estimated that the maximum thickness of the oil film was 1.63nm — and, by extension, that this measurement might estimate the diameter of a single molecule of olive oil.[28] By January 1891, Pockels, having either read or heard of his interest in thin oil films, wrote a twelve page letter to Rayleigh, describing her tin trough apparatus and the variability of the surface tension of

26. Katharina Al-Shamery, "Agnes Pockels (1862-1935)," in *European Women in Chemistry*, ed. Jan Apotheker and Livia Simon Sarkadi (Weinheim: Wiley-VCH Verlag, 2011), 35–38; see also Gabriele Beisswanger, "Das Portrait: Agnes Pockels (1862-1935) und die Oberflächenchemie," *Chemie in unserer Zeit* 25, no. 2 (April 1991): 97–101. For contemporary celebrations of Pockels' work, see: Lord Rayleigh, "Investigations in Capillarity," *Philosophical Magazine* 5th ser., vol. 48, no. 293 (October 1899): 321–37; on the award of the Laura R. Leonard prize of the *Kolloid-Gesellschaft*, Wolfgang Ostwald, "Die Arbeiten von Agnes Pockels über Grenzschichten und Filme," *Kolloid-Zeitschrift* 58, no. 1 (1932), 1-8.

27. Lord Rayleigh, "Measurements of the Amount of Oil Necessary in Order to Check the Motions of Camphor upon Water," *Proceedings of the Royal Society of London* 47 (1890): 364–67. For Rayleigh's and Evelyn's Balfour's "homemade" science see Donald L. Opitz, "'Not Merely Wifely Devotion': Collaborating in the Construction of Science at Terling Place," in *For Better or For Worse? Collaborative Couples in the Sciences*, ed. Annette Lykknes, Brigitte Van Tiggelen, and Donald L. Opitz (Basel: Springer Basel, 2012), 33–56.

28. In late-nineteenth century notation this would be 1.63 *μμ*.

contaminated water. Rayleigh immediately forwarded the letter to *Nature* for publication, securing Pockels' high standing among physicists.[29]

Remarkably for a bathtub experiment, Rayleigh's measurement for the diameter of an oil molecule was only slightly refined in the next two decades. This measurement, and this confluence of experiments on surface tension and molecular dimensions, happened in a relatively lowly domain of physics, far from the rarified realms of abstruse thermodynamic equations or metaphysical debates. The French chemist Henri Devaux (1862–1956), for example, performed demonstrations and experiments on thin oil films with a tiny toy boat.[30] What they had in common was a continuing operative assumption that molecules could be treated mathematically as perfect spheres — after all, this is the only way one could assume a molecule has a diameter, rather than a length, width, and height.[31] The physical assumption of spherical molecules in turn affected the way Rayleigh interpreted Pockels' discovery of the effects of oil on the surface tension of water. Pockels had found in the 1880s that the surface tension of water dropped when contaminated with oil, but surprisingly there was no clear linear or geometrical relationship between the amount of oil and the decrease in surface tension (Figure 5.5b). As Pockels slowly added oil to the water's surface, surface tension remained unchanged until a certain amount of oil was on the surface; then it plummeted sharply in relation to the amount of oil, but before long the drop in surface tension leveled off, decreasing only slowly. Rayleigh suggested that the sudden drop in surface tension was due to the effects packing the spherical molecules in an increasingly tight space, as well as the different forces at work between the

29. Agnes Pockels, "Surface Tension," trans. Lord Rayleigh, *Nature* 43, no. 1115 (March 12, 1891): 437-439.

30. Henri Devaux, "Mouvements spontanés des certains corps a la surface de quelques liquides," *La nature: revue des sciences et de leurs applications aux arts et à l'industrie* 16, no. 777 (1888): 331–34; and Henri Devaux, "Oil Films on Water and on Mercury," *Annual Report of the Smithsonian Institution, 1913,* 261–73.

31. While the exact nature of these molecular spheres was a matter of debate, their sphericity was not; see, for example, Elizabeth Garber, "Molecular Science in Late-Nineteenth-Century Britain," *Historical Studies in the Physical Sciences* 9 (1978): 265–97.

oil molecules and the water's surface. The sharp decrease in surface tension "must depend upon the forces supposed to be operative between the molecules of oil. If they behave like the smooth rigid spheres of gaseous theory, no forces will be called into play until they are closely packed." Rayleigh's well-hedged conclusion was that the sharp drop in surface tension occurred as the oil film on the water's surface transitioned from being one molecule thick to two molecules thick. Any heterogeneity in the olive oil might then explain the differences across measurements, "whereby some molecules would mount more easily than others" in the chaotic, jumbled transition state.[32]

c. *Interpreting surface tension: molecular orientation*

This confluence of surface tension measurements and molecular hypotheses would lead two different American physical chemists to independently and simultaneously develop the theory of molecular orientation in 1917.[33] Irving Langmuir (1881-1957) and William Draper Harkins (1873-1951) knew each other professionally, and the timing of their announcements in the *Journal of the American Chemical Society* (*JACS*) a mere five months apart led to a bitter priority dispute and accusations against Harkins of intellectual theft.[34] Even though Harkins and Langmuir eventually

32. Lord Rayleigh, "Investigations in Capillarity," 337.

33. By 1917 surface tension was understood mathematically as a proxy for the free energy of a physical system, but surface tension remained as the focus of measurements and experiments.

34. The bitterness of the priority dispute between Harkins and Langmuir lasted for quite some time, and signs of the dispute can be seen in many of their publications and citations. At one point Harkins was so intent on bolstering his priority claim that in a 1924 textbook chapter he reproduced a page from one of his student's lecture notes from 1914 (William D. Harkins, "Surface Energy in Colloid Systems," in *The Theory and Application of Colloidal Behavior*, vol. 1, ed. Robert Herman Bogue [New York: McGraw-Hill, 1924], 153, fig. 5); the note is far from convincing. By 1918 Langmuir was writing in the *JACS* that he had developed the idea in 1916, but that Harkins "elaborated" the theory of molecular orientation in March 1917, at least suggesting he thought Harkins' work was neither insubstantial nor unoriginal; see for example Irving Langmuir, "The Adsorption of Gases on Plane Surfaces of Glass, Mica and Platinum," *JACS* 40, no. 9 (1918): 1361–1403. Harkins preferred to point out that the British colloid chemist William Bate Hardy had glancingly suggested the idea of molecular orientation in print in 1912; see W. B. Hardy, "The Tension of Composite Fluid Surfaces and the Mechanical Stability of Films of Fluid," *Proceedings of the Royal Society of London* A, 86, no. 591 (1912): 610–35, especially 634.

Patrick Coffey has shown that several of Harkins' contemporaries thought that Harkins showed a pattern of intellectual theft, although Coffey is quite intent on highlighting the discord between American scientists in this period;

agreed on the principle and theory of molecular orientation, their approaches to molecular orientation were quite different, and addressed to slightly different scientific communities. Harkins, a relatively traditional university chemist, wrote and spoke in part to colloid chemists, a new and rapidly growing discipline that counted many biologists in its ranks. Langmuir, on the other hand, cemented his reputation as an iconoclastic and revolutionary chemist who endeavored to unify and clarify differences between physical and chemical approaches to atoms and molecules.

Langmuir had trained in Walther Nernst's eclectic physical laboratory in Göttingen, but in 1909 he joined General Electric's new research laboratory in Schenectady, New York, eschewing a traditional academic career.[35] At GE Langmuir was free to pursue whatever interested him (unusual for a corporate scientist), and this would eventually include research on thin films and atomic structure in lightbulb design. His most important agenda in the 1910s and '20s was bridging what he saw as a yawning chasm between chemical and physical theories of molecular behavior, asserting that chemists' structural formulae — formulae that did not suggest perfect, spherical symmetry — ought to have a greater bearing on theories of physical structure and behavior. Rayleigh and Pockels' experiments with oil films provided the opportunity to build that bridge.

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see Patrick Coffey, *Cathedrals of Science: The Personalities and Rivalries That Made Modern Chemistry* (London: Oxford University Press, 2008), 128-134. In my judgement Coffey's claim for Harkins' dishonesty rings true, but many outsiders happily cited Langmuir and Harkins together (and occasionally Hardy as well) as developing and elaborating the theory of molecular orientation; these included James W. McBain and Henri Devaux. This may have been either out of ignorance or out of support for Harkins; a few physical chemists, including N. K. Adam, conspicuously avoided citing Harkins and his team while showering Langmuir with praise.

35. For such an important figure in the history of chemistry, biographical studies of Langmuir are surprisingly limited to obituaries and biographical memoirs from the 1950s, and a few dictionary entries. See Charles Süsskind, "Langmuir, Irving," in *Complete Dictionary of Scientific Biography*, vol. 8 (Detroit: Charles Scribner's Sons, 2008), 22–25. Robert Kohler's classic essay is one of the few to study Langmuir's theories and scientific style in detail; see "Irving Langmuir and the 'Octet' Theory of Valence," *Historical Studies in the Physical Sciences* 4 (1974): 39–87. There are also some sociological studies of industrial chemistry that examine Langmuir's tenure at GE, see George Wise, "Ionists in Industry: Physical Chemistry at General Electric, 1900-1915," *Isis* 74, no. 1 (1983): 7–21; and, "A New Role for Professional Scientists in Industry: Industrial Research at General Electric, 1900-1916," *Technology and Culture* 21, no. 3 (1980): 408–29; Leonard S. Reich, "Irving Langmuir and the Pursuit of Science and Technology in the Corporate Environment," *Technology and Culture* 24, no. 2 (1983): 199–221.

Langmuir used what was essentially a more elaborate version of Pockels' tin trough, repeating many of Pockels' and Rayleigh's experiments on surface tension. The key difference was that Langmuir used very specific and chemically pure oils, rather than whatever brand of olive oil happened to be in the kitchen, as Lord Rayleigh had in 1889. Langmuir observed that most oils decreased the surface tension of water by the same amount when they were laterally compressed, but that, with uncompressed films, this ability to lower surface tension depended on exactly what kind of oil was being used. He believed that the specific composition of a fatty acid's hydrocarbon chain and the number of double bonds in that chain corresponded with the ability to stretch a monomolecular film without breaking it — and indeed Langmuir found that the saturated stearic acid covered a maximum area that was less than half of a film covered by the monounsaturated oleic acid.[36] Langmuir concluded by arguing that a single molecule of oil resting on a water surface had its carboxyl group and any unsaturated carbon double bonds chemically bonded to the water, while the CH_3 hydrocarbon tails flopped around freely on the surface.[37] Thus when the oil was compressed, only the carboxyl groups remained stuck to the surface of the water, while the hydrocarbon tails stood vertically upright. In other words, Langmuir found an experimental system that could show that fats with different chemical formulas could be found to have different lengths, and that there were two different kinds of relationships between surface tension and length: there was the relationship between the length of the fatty acid and the changes in surface tension, but there was also a less direct relationship between the level of chemical saturation in the fatty acid and the

36. For example Langmuir reported that a molecule of oleic acid ($C_{17}H_{33}COOH$) occupied an area of $46\times10^{-16}cm^2$, while a molecule of the stearic acid ($C_{17}H_{35}COOH$) covered a surface area of only $22\times10^{-16}cm^2$. Irving Langmuir, "The Constitution and Fundamental Properties of Solids and Liquids. II. Liquids.," *JACS* 39, no. 9 (1917): 1848–1906.

37. Today we would consider such contact due to "physical" van der Waals forces, but in 1917 Langmuir firmly believed that these forces were due to chemical valence, because they were related to the specific chemical formulae of the oil.

changes in surface tension. The specific chemistry of fats, Langmuir argued, seemed to override the more general assumptions made in physics.

Langmuir's series in the *JACS* was brilliant in synthetic scope, but also difficult to understand in all of its details unless one had as wide-ranging a command of chemical and physical theory as Langmuir had. In contrast, Harkins' work on surface tension relied less on synthesizing a wide range of theories and more on tackling a specific problem: the relationship of surface tension to solubility. For example, theories relating surface tension and solubility suggested that urea and water enter into solution very easily because they have extremely low surface tension, while oil and water are so insoluble one can see the surface tension working with the naked eye. However, Harkins and his laboratory team at the University of Chicago discovered that surface tension alone was a poor predictor of solubility, especially of fats and other organic acids. Harkins' team surveyed surface tension data for 336 different substances at both air and in water, and noticed that for many substances the surface tension of one substance in the air was drastically different than if it had an interface with water.[38] Furthermore, the differences seemed to be roughly related to the presence of carboxyl (COOH) groups and the relative saturation of any hydrocarbon chains. However, rather than make any general argument about the length of a molecule, or hydrocarbon chains flopping around on water, Harkins proposed a very physicalist thought experiment, asking: How much work would it take to separate two substances, say, benzene and water, at their interface?

38. The data were published in William D. Harkins, F. E. Brown, and E. C. H. Davies, "The Structure of the Surfaces of Liquids, and Solubility as Related to the Work Done by the Attraction of Two Liquid Surfaces as They Approach Each Other (Surface Tension V.)," *JACS* 39, no. 3 (March 1917): 354–64; and more comprehensively William D. Harkins, Earl C. H. Davies, and George L. Clark, "The Orientation of Molecules in the Surfaces of Liquids, the Energy Relations at Surfaces, Solubility, Adsorption, Emulsification, Molecular Association, and the Effect of Acids and Bases on Interfacial Tension (Surface Energy VI.)," *JACS* 39, no. 4 (April 1917): 541–96. The Harkins lab used a much more precise and complex instrument than the Pockels-Langmuir trough: see William D. Harkins and F. E. Brown, "A Simple Apparatus for the Accurate and Easy Determination of Surface Tension, with a Metal Thermoregulator for the Quick Adjustment of Temperature," *JACS* 38, no. 2 (1916): 246–52.

> If it is imagined that a single liquid is divided into two parts by a horizontal plane, and that when this imaginary plane is lifted the upper layer rises with it, then, where before there was no surface, two surfaces now appear…If the two surfaces now approach and meet one another, this free energy disappears, since there is now no surface energy at the imaginary interface.[39]

Or, stated in more formal terms: If the surfaces of two separate substances are maintained by a certain amount of energy, then what is the decrease in energy of two substances as they approach one another? This gave the mathematical expression:

$$(\gamma_a + \gamma_b - \gamma_{ab} = -\Delta\gamma)$$

where γ_a and γ_b were the surface tension measurements of substances *a* and *b* independently in air or water, and γ_{ab} was the surface tension of *a* and *b* when they were in contact with each other. If there was difference remaining, $-\Delta\gamma$, it would suggest that there was something about the interface of the two liquids that was very different from the behavior of the two liquids acting independently of one other. Harkins argued that if there was any non-zero value for $-\Delta\gamma$, then in order to make the transition from *a* to *b* less abrupt the molecules could be imagined to orient themselves in a way that lowered the tension at the interface. As he put it in a more general way: the boundary of any homogenous liquid with another must have some structure to make the boundary less energetic, if possible.

Harkins concluded that, "At the interface between another liquid and water, the molecules in the surface of the liquid set themselves in such a way as to turn their more active or polar groups toward the surface of the water. At such surfaces liquids therefore show a structure."[40] Harkins' explanation for the energetic difference at the interface was thus the same as Langmuir's explanation of the relationship between surface tension and the maximum area of a monomolecular oil film:

39. Harkins, Brown, and Davies, "The Structure of the Surfaces of Liquids," 355.

40. *ibid.*, 363.

there must be some shape or other kind of polarity in molecules that causes them to orient at the interface, and this orientation worked to reduce surface tension.

d. Colloid chemistry and the iconography of molecular orientation

Conceivably, Langmuir's position at General Electric insulated him from other scientists who needed to understand how his theory might be generally applicable: he was a lone genius given free rein in a corporate laboratory, and the truly eclectic nature of his writings seems to reflect the wide range of interests he held in a somewhat undisciplined fashion. Harkins' writings and lectures were only slightly less difficult, but he was to prove more capable than Langmuir of speaking and writing to audiences who did not have much use for either mathematical physics or the details of organic chemical theory. Not only was Harkins less dogmatic in his views, but he was more closely engaged with the broad, eclectic interests and concerns of colloid chemistry (see Chapter 3).

It was perhaps this kind of wider engagement that led Harkins to give those less mathematically or theoretically inclined colloid chemists a series of verbal and graphical analogies for molecular orientation, starting in his June 1924 lecture to the National Colloid Symposium hosted by Northwestern University.[41] Harkins' lecture, "The Orientation of Molecules in the Surfaces of Liquids," contains the first graphical representation of molecules as a ball and stick, to illustrate his surface structure principle from 1917. The sheer novelty of the concept of molecular orientation, however, gave cause for Harkins to elaborate two analogies in the lecture. One was verbal:

41. This was the second such symposium organized by the National Research Council, and topics for the eight symposia held between 1923 and 1930 varied widely from theoretical considerations, instruments, and to applications of colloid theory in engineering and biology. The 1924 Colloid Symposium, for instance, had papers on the rubber industry, new instruments, soil science, theories of emulsification, a whole paper on iodine, bacteriology, physiology, and an extensive rebuttal of Jacques Loeb's recent work on the Donnan equilibrium in protein solutions.

> The ordinary observation of large scale objects, such as logs or ships, as they lie on the surface of a body of water, indicates that these objects exhibit a characteristic orientation with respect to the surface. Thus logs, when not too closely crowded together lie flat upon the water, that is the longitudinal axis is parallel to the surface. However, if one end of each log is loaded with a mass of iron or brass of the proper weight, it floats upon the surface and the longitudinal axis becomes vertical.[42]

This exercise in imagination was then accompanied by a visual/material analogy, physically dragged out onto the stage in front of the audience at Northwestern. As the published text in the *Colloid Symposium Monograph* described the scene parenthetically,

> (These phenomena were illustrated by the use of a large number of cylindrical sticks of wood 3 mm. in diameter and 14 cm. long, weighted by a small cylinder of brass placed at one end. These were thrown upon the surface of the water in a large glass cylinder. This is represented in a diagrammatic way in Fig. 1. One of the vertical sticks was taken from the water, the brass weight removed, and the stick dropped upon a vacant space upon a water surface. At once this assumed a horizontal position, thus exhibiting another type of orientation.)[43]

The first figure in the lecture is static (Figure 5.6, left), and claims to represent the analogy of weighted logs floating on water.

By equal measure Harkins also emphasized that his diagrams were "highly conventionalized," and in some of the diagrams it is not clear whether the diagrams were supposed to illustrate the molecules themselves, or rather illustrate dissymmetrical fields of molecular and surface forces.[44] Yet the potential for slippage into realism was clear, and some of Harkins' other figures (Figure 5.6, right) seem to show how a jumbled mass of butyric acid molecules really could behave — individual molecules plunging into the water and tumbling back out, some molecules curved and other straight, most of the surface molecules neatly oriented, and a few molecules left out of the orientation party. Such a figure was supposed to illustrate Harkins' argument that "disorder has been overemphasized" in thermodynamic conceptions of molecules in liquids. Yet in attempting to illustrate a semi-ordered system, structured at the surface but unstructured in the greater body,

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42. William D. Harkins, "The Orientation of Molecules in the Surfaces of Liquids," *Colloid Symposium Monograph* 2 (1924): 141–73.

43. *ibid.,* 141–42.

44. *ibid.*, 149.

Harkins managed to produce schematic diagrams that were realistically suggestive precisely because of their liveliness.

It is not clear exactly how or when Harkins' diagrams began to move their way through other parts of colloid chemistry. By now he was well known as a leading authority on surface forces, and versions of the Colloid Symposium lecture found their way into two colloid chemistry textbooks. In the first textbook, published in 1924, Harkins even mentions that polar molecules "have been represented in this laboratory for many years" by the ball and stick symbol, though this is the only place where he makes this claim.[45] (This is also the only place where Harkins credits his student Ernest B. Keith with the illustration.) In the second textbook, part of the very influential multi-volume series edited by the colloid chemist Jerome Alexander, Harkins not only reproduces all of the diagrams from 1924, but ceases to refer to them as "conventions." Langmuir also wrote a chapter for Jerome Alexander's textbook, and this chapter seems to have been the first time Langmuir resorted to using a diagrammatic representation for molecular shape and dissymmetry, at least in print. Rather than use a version of Harkins' diagram, Langmuir here used a small black dot connected to a fat, elongated tube, like a caper stuck to one end of a sausage, with the tubes varying in length to represent the real length of the molecule in question (Figure 5.7).[46] Few if any later diagrams look like Langmuir's 1926 diagram, which would have been more useful in illustrating molecular dimensions than the larger-scale, aggregate effects of molecular orientation.

Harkins was more than just as an authority on surfaces, however. By the mid-1920s, surfaces became a central organizing theory in colloid chemistry, with "colloids" themselves being redefined as systems that were composed of both a vast amount of surface and a large number of surfaces.

45. Harkins, "Surface Energy in Colloid Systems," 154.

46. Irving Langmuir, "The Effects of Molecular Dissymetry," in Jerome Alexander, ed., *Colloid Chemistry: Theoretical and Applied* (New York: Chemical Catalog Co., 1926), 538.

Earlier in the twentieth century, colloids had been redefined from an operational state (*e.g.*, inability to crystalize, inability to pass through parchment paper) to being a "disperse, polyphase system," a mixture of multiple substances with different chemical identities (*e.g.*, mud is a mixture of a watery "continuous" phase and a "disperse" mineral particulate phase).[47] The physicist Herbert Freundlich (1880-1941) quickly recognized that this definition of colloids as disperse, polyphase systems meant that a colloid was generalizable as a gigantic surface: each particle of the disperse phase would have an exterior surface that remained in contact with the continuous phase, with the total surface between the two phases measurable in the range of tens to hundreds of square meters in a single cubic centimeter of a colloid substance.[48] By June of 1926 the soap and colloid chemist James W. McBain (1882-1953) stood as the keynote speaker of another Colloid Symposium, now hosted at MIT, and argued that surface tension was the ultimate determinant of colloidal stability: "It is not the nature of the interior," he declared, "but the composition of the exterior of the particle that determines [the colloid's] chief properties and degree of stability…The motto of the colloid is, 'Save the surface, and you save all.'"[49]

The very first case I have found where the ball and stick image was used by someone other than Harkins dates from just one month prior to McBain's Colloid Symposium address in 1926. This was also by McBain, in May of 1926, in a very technical physical lecture on "An Experimental Test of the Gibbs Adsorption Theorem" (Figure 5.8).[50] McBain used a single, four-part

47. See Chapter 3, section *a,* above.

48. See Herbert Freundlich, *Kapillarchemie und Physiologie: Habilitations-vorlesung gehalten am 29. Oktober 1906* (Dresden: Steinkopff & Springer, 1907); and Herbert Freundlich, *Kapillarchemie: Eine Darstellung der Chemie der Kolloide und verwandter Gebiete* (Akademische Verlagsgesellschaft, 1909).

49. James W. McBain, "A Survey of the Main Principles of Colloid Science," *Colloid Symposium Monograph* 4 (1926): 7–18.

50. James W. McBain and George P. Davies, "An Experimental Test of the Gibbs Adsorption Theorem: A Study of the Structure of the Surface of Ordinary Solutions," *JACS* 49, no. 9 (1927): 2230–2254. The paper was read at the Mid-West Regional Meeting of the American Chemical Society in Madison, Wisconsin in May 1926, and sent for publication in late July/early August of 1927.

"diagrammatic representation" of a monomolecular film, copying Harkins', not Langmuir's diagrams. McBain and his student George Davies created this diagram to compare some of the discrepancies between Langmuir's 1917 basic theory (*a* in the diagram), other explanations coming from thermodynamic theory (*b* and *c*), and attempted measurements of how many molecules seemed to actually be adsorbed to the surface, as well as how *deep* the surface layer could be (*d*). Harkins is not cited as a source for the image, and McBain and his student George Davies only note that Harkins and several others, had offered "a clear picture of the structure of films of insoluble materials resting upon a solvent such as water."[51]

McBain's use of the ball and stick to represent a molecular film is quite casual and unattributed, so it is impossible to specify exactly from where he might have borrowed the image, or whether he invented the image himself. However, it seems very likely that the images have the same provenance, given the importance of Harkins' and Langmuir's writing, and given that McBain was a contributor in both of the textbooks for which Harkins had also written. McBain's own work in soap chemistry offers another possible route of transmission connected with Harkins: many of Harkins' 1924–25 articles engaged with soap chemistry, and in this context he briefly suggested the ball and stick model actually represented molecular "wedges" capable of orientation.[52] In 1925, in a semi-popular lecture to the Royal Institution, McBain had described colloidal soap particles as

> like a pair of military hair brushes, in which the bristles represent the hydrocarbon chains of the molecules arranged parallel to each other in sheets, two such layers being put together hydrocarbon to hydrocarbon. The two backs of the brushes on the outside represent the hydrate layer and the un-ionised electric double layer.[53]

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51. *ibid.*, 2230. McBain probably meant "picture" figuratively as a "conception" rather than literally as an "image" or "visual representation"; he cites Rayleigh, Adam, Devaux, Langmuir, and Harkins, and of these scientists by May 1926 only Harkins had published an image of surface molecules.

52. It is of course possible that Harkins himself got the idea from McBain or someone else working in soap chemistry; however, later in the 1940s Harkins entered the physical chemistry of soaps in his own right.

53. James W. McBain, "Soaps and the Theory of Colloids," *Notices of the Proceedings at the Meetings of the Members of the Royal Institution* 24 (1925): 579–84.

This picture of an opposing pair of brushes was accompanied by an elaborately detailed chemical diagram that suggested a precise location for every atom and valence bond, a mesmerizing arrangement of capital H's and C's in neat, parallel zig-zags and rows — an image more useful for showing detailed structure that for illustrating orientation or surface structure (Figure 5.9).[54] This connection between Harkins and soap chemistry was also probably not an accident: McBain saw the study of soap and soap production as an especially rich area for colloid chemistry, since soaps were chemically simple substances that were but poorly understood in their manifold physical behaviors.

Even more evocatively, McBain also cheerfully suggested that the colloidal particles of soap "resembles a group of, say, less than a dozen eels tied together by the tails, and pointing outwards in all directions from the common centre."[55] Although there was some precedent to describing fat molecules as having hydrocarbon "tails" before 1925 (Langmuir used the word "tail" once in his 1917 article), the verbal convention of referring to lipids as having "heads" as well became common enough that an older soap chemist thought it merited some disparaging comments:

> The individuality of soap molecules is so peculiar that they may be described as eccentric. By various workers they have been credited with heads and tails, although they prefer to stand upon the former. Indeed, they appear to try to emulate the ostrich and bury their heads in the most unlikely surfaces while the rest of their body, which only consists of a tail, sticks up in the air. This type of anthropomorphic familiarity, however picturesque, should only be indulged in with caution…[and] the implied endopsychic endowment of the molecules is quite unjustifiable.[56]

This particularly ill-tempered soap chemist, A. S. C. Lawrence, was probably, as Max Stadler has argued, the first to publish an illustration of a "sandwich" of fat molecules, with tails oriented towards each other, and using the ball-and-stick convention (Figure 5.10).[57] This image was copied

54. There is a much deeper history connecting membranes to soap chemistry, and I am very much indebted to Max Stadler, "Assembling Life: Models, the Cell, and the Reformations of Biological Science, 1920-1960" (Ph.D. dissertation, Imperial College, University of London, 2009).

55. James W. McBain, "Soaps and the Theory of Colloids," 582.

56. A. S. C. Lawrence, *Soap Films: A Study of Molecular Individuality* (G. Bell And Sons, Ltd., 1929), 132.

57. Max Stadler, "Assembling Life," 73–74.

and cited in 1930 by Neil Kensington Adam (1891–1973), the physical chemist who was the mentor and advisor to the "inventor" of the lipid bilayer cell membrane in 1935.[58]

When James Danielli proposed his cell membrane model in 1935 — a layer of protein adsorbed onto the lipid bilayer that "would have been obvious to any competent physical chemist" — he had already spent seven years under Adam's tutelage at University College London, having gone to Adam for chemistry lessons since 1928, at the precocious age of seventeen.[59] So it should be no surprise that Danielli thought a bilayer of lipid molecules was an obvious structure that needed no citation. The closest citation for a lipid bilayer in Daneilli and Davson's short and quite speculative 1935 paper is to Adam's 1930 textbook, *The Physics and Chemistry of Surfaces*, where the only molecular diagram was the one borrowed from Lawrence.[60]

e. *Lipids, fiber chains, and the molecular biological microworld*

Wilhelm J. Schmidt's education in molecular orientation and in molecular imagery more broadly seems to have happened very quickly, much of it taking place in 1938. His first written statements about molecules and molecular structure came in a two-part article in July and August of 1938 *Naturwissenschaften* (a general science journal similar to *Science* and *Nature*); this was followed by a more specific lecture on frog eye retina structure to a meeting of the *Kolloid-Gesellschaft* devoted to medical and biological issues in September.[61] According to his citations in 1938–39, Schmidt relied heavily on a 1931 review essay by Henri Devaux, work by the Dutch colloid chemist H. G.

58. *ibid.*; and Neil Kensington Adam, *The Physics and Chemistry of Surfaces* (Oxford: Clarendon Press, 1930), .

59. W. D. Stein, "James Frederic Danielli. 13 November 1911-22 April 1984," *Biographical Memoirs of Fellows of the Royal Society* 32 (1986): 117–35.

60. Max Stadler, "Assembling Life," 73–74.

61. W. J. Schmidt, "Molekulare Bauweisen tierischer Zellen und Gewebe und ihre polarisationsoptische Erforschung," *Naturwissenschaften* 26, no. 30–31 (July–August 1938): 481–90, 509–14; W. J. Schmidt, "Polarisationsoptische Analyse eines Eiweiß-Lipoid-Systems, erläutert am Außenglied der Sehzellen," *Kolloid-Zeitschrift* 85, no. 2/3 (1938): 137–48.

Bungenborg de Jong, and the 1933 book *The Fundamentals of Fibre Structure*, a collection of popular lectures by English physicist William T. Astbury (1898–1961).[62]

Astbury's work in particular provided both imagery and rhetoric that broadened Schmidt's previous notion of *Bausteine*, or brick-like, micellar building blocks. Whereas in 1937 Schmidt had used Ambronn and Frey-Wyssling's models and images of micellar fiber structures, in 1938 Schmidt began to use Astbury's images of long chain molecules instead (Figure 5.11). Astbury was quite blunt about his dislike of theories of fiber structure that had any hint of colloidal theory in them. Quite forgetting the longer history of x-ray diffraction research in 1920s colloid chemistry, Astbury argued that,

> Textile fibers were said to be not crystalline but 'colloidal', in accordance with a distinction that has now disappeared. X-rays have abolished such a distinction once and for all. We still preserve some vague line of demarcation for convenience of study, but it is now definitely established that almost all those substances which used to be described as non-crystalline or colloidal, even things like gelatine, muscle, or india-rubber, are undoubtedly crystalline to a greater or less extent, especially when under tension. We may say that the crystalline state is the natural state of solid matter…Any collection of molecules in the form of a three-dimensional pattern, however small, constitutes a crystal and will reflect X-rays in a more or less regular manner.[63]

Thinking of fibers in terms of long, crystalline chains changed the way Schmidt interpreted the birefringence of long, fiber-like structures. Astbury's molecular theory offered a new way to think about the structure of cross-sections of fibers bundled into thicker strands in different ways (Figure 5.12, left). More consequential, however, was Schmidt's realization that an idea of long fiber structure could be used to rethink the structure of protein films and networks — not as a random assortment of platelet- or rodlet-shaped protein micelles, but as a mats of fibers running every which way (Figure 5.12, bottom). This idea of mats of fibers allowed Schmidt to think of large-scale, fibrous structures as appearing isotropic and random when viewed in one direction, but anisotropic

62. Henri Devaux, "Les lames très minces et leurs propriétés physiques," *Journal de physique et le radium* 2, no. 8 (1931): 237–72; H. G. Bungenberg de Jong and J. Bonner, "Phosphatide Auto-Complex Coacervates as Ionic Systems and Their Relation to the Protoplasmic Membrane," *Protoplasma* 15 (1935): 198–218; W. T. Astbury, *Fundamentals of Fibre Structure* (London: Oxford University Press, 1933).

63. W. T. Astbury, *Fundamentals of Fibre Structure*, 77–78.

and similar to platelets when viewed in a different direction. In addition, this completely changed the way Schmidt imagined the microphysics of stretching: whereas in 1935 he had imagined a stretched protein structure as micellar blocks becoming shorter and wider or longer and narrower (Figure 5.13a), in 1939 he imagined such a structure as a coiling or an ordering and reordering of fibers (Figure 5.13b).

What would have been completely foreign to fine structure theorists like Frey-Wyssling was Schmidt's complete reliance on a visually-inspired language and drawings of shapes of molecules, and this was especially true of the way he treated the molecular orientation of lipids. The phrase "surface tension" ("*Oberflächungspannung*" and variations thereof) appears only three times and but very briefly in Schmidt's first article featuring lipid molecules in the *Naturwissenschaften* article (Figures 5.14a and 5.14b). When he spoke at the *Kolloid-Gesellschaft* a the next month, he took out any mention of "surface tension" entirely — an odd move, given the journal. What he did include were two diagrams of the fine structure of the frog eye retina, incorporating both the ball-and-stick image of lipid structure as well as a roughly sketched iteration of the fibrous protein structure (Figure 5.15, right). This was not the first time that Schmidt had revisited the frog eye retina structure: in 1937 he had created another structural diagram (which he had not done in 1935), still within the graphical idiom of micellar structure (Figure 5.15, left)

The molecular diagrams quickly became more than simply reinterpretations of polarization microscopic evidence. Schmidt's 1939 lecture on the molecular structure of the cell was followed up by a much more extensive demonstration and lecture across two days of the 1939 meeting of the German Zoological Society, on August 1–2 in the Baltic city of Rostock.[64] The fiber diagram noted above (Figure 5.12, bottom) was one of the many Schmidt was now using to actively predict the

64. W. J. Schmidt, "Polarisationsoptische Erforschung des submikroskopischen Baues tierischer Zellen und Gewebe: Der experimentelle Weg und einige Beispiele," *Verhandlungen der Deutsche Zoologische Gesellschaft* 41 (1939): 303–89.

kinds of birefringence patterns one ought to *expect*, given what was known about molecular structures — or, rather, given how Schmidt illustrated molecular structures. This was indicated by the index-ellipses on many of the schematic diagrams, showing how an aggregated structure of many different kinds of materials could be interpreted. Rather than immediately asking his audience to look at living tissues, Schmidt offered a few hypothetical diagrams for protein-lipid structures, before embarking on a series of exercises with chitin, collagen, and lecithin smears. The exercises using exemplary materials were aimed at training novice polarization microscopist to notice what kinds of materials and under what conditions certain birefringence patterns could appear. The diagrams in the article were then meant to illustrate the fine structural details that were causing the birefringence patterns. For Schmidt in 1939, molecular structures could be "seen" by inference and even manipulated on a large scale, regardless of whether the individual molecules are visible or yet rendered on the page.

The last time Schmidt would be able to write about his methods in depth came in 1941. Soon afterwards, the Second World War left the Giessen zoological institute devoid of all but a few graduate students; the American firebombing campaign on December 6, 1944 would level most of the city, including Schmidt's library, laboratory, and much of the rest of the university as well.[65] In 1941 Schmidt now had the experience and confidence to freely draw and diagram what he thought were the behavior and structural inclinations of proteins and lipids. These 1941 drawings were clearly meant to be a realist images of what he imagined was the fine structure of lipid membranes (Figure 5.16).

> *Strong hydrophilic lipoids* such as *lecithin* order themselves automatically in the presence of water into bimolecular layered systems, so-called *myelin figures*: attracted by the hydrophilic groups, water penetrates into the material and gives the molecules freedom of movement…the ones at the surface

65. W. J. Schmidt to Albert Frey-Wyssling, 8 May 1946, HS 443:1059, Frey-Wyssling, Albert, Briefe, Hochschularchiv der ETH Zürich; and Wilhelm J. Schmidt, "Aus meiner Werkstatt," 233.

> turn their hydrophilic poles against the water and parallelize themselves; the resulting unimolecular lamellae produce the structure of a second one with a reversed orientation of its molecular poles (see left and right sides of the illustration) and in this way the process continues.[66]

Not only is the diagram of a mass of lecithin in water especially evocative in its dynamics: the language Schmidt uses to animate the lipid molecules is built on reflexive verb constructions to give the molecules agency and individuality, as well as reality. The ball and stick lipids are actively sorting themselves out, "*parallelisieren sich*," from a chaotic jumble in the middle of the mass and into orderly bi- and tri-layers at the outer edge — a droplet of lecithin rendered in fine molecular detail.

But it was Schmidt's fully molecular image of the multi-layered lipid system (known as a "myelin figure," after which the "myelin sheath" was later named) and the protein-lipid system that shows how far the iconography of lipids had come as a scientific tool (Figure 5.17). These diagrams were more than just representations: they were tools for disaggregating all of the different molecular parts, their arrangements, and their relationships to one-another. The ovals laid on top of each figure were meant to indicate form (F) and intrinsic (E) birefringence of the system. With up to four bilayers in the system, Schmidt indicated that at first glance the multi-layered lipid system would show form birefringence along the length of the lipid figure, corresponding to the rows of the lipid heads. But, by drawing out the lipid bilayer structures, Schmidt was able to show that the intrinsic birefringence — the arrangement and orientation of each individual molecule — is actually perpendicular to the axis of the myelin figure, even as the overall structure appears as parallel lines along length of the tube. And in the case of the protein-lipid system, Schmidt explained that not only did the lipid system (L) have its own form and intrinsic birefringence patterns (hence the labels

66. W. J. Schmidt, "Die Doppelbrechung des Protoplasmas und ihre Bedeutung für die Erforschung seines submikroskopischen Baues," *Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie* 44, no. 1 (1941): 44, original emphasis.

E|L and F|L), but so too did the protein layer (E|P and F|P), and the entire lipid-protein system as well (F|P+L).

f. Conclusion

The most crucial feature of these images of lipid and lipid-protein systems in Figure 5.17 is that they expect an exact correspondence to nature, at a scale where forces and entities are fundamentally inaccessible to direct observation. Polarized light microscopy could only shows signs of directional orientation and distinguish among material systems with patterns of light or through flashes of color; it was at best an indirect method of seeing fine structure, a theory-laden vision that relied heavily on the microscopist's intuition and experience. Equipped with the iconography of molecular theory, Schmidt could draw out different molecular structures, and look for the structure that could most convincingly explain those patterns of light and flashes of color. At the same time, Schmidt's images, perhaps even more than his observations, became arguments that the biological microworld really *was* structured in the ways he described and illustrated on paper. Having accepted Schmidt's images as a true reflection of nature, any other observer could see the patterns of birefringence under the polarized light microscope as affirming the molecular reality shown on the page. As John Marrinan and Michael Bender have argued, in their exploration of diagrams in Diderot's *Encyclopédie,* "Diagrams incite a correlation of sensory data with the mental schema of lived experience that emulates the way we explore objects in the world. They are closer to being things than being representations of things."[67] A belief in biological, molecular reality could create such images, but such images also help someone vividly imagine and believe in that same molecular reality. He could confidently rely on the image of the self-orienting lipid molecule to show his grasp of the laws of physics and chemistry, while also feeling no need to actually address the complex physical forces and dynamics that governed that molecule's individual behavior. At the same time, Schmidt's diagrams followed the iconographic conventions of the molecular theories that came out of physics and colloid chemistry. An image like the one Schmidt created in Figure A made the argument that the protoplasm's structure could be imagined to be built entirely by small repeating

67. John B. Bender and Michael Marrinan, *The Culture of Diagram* (Stanford: Stanford University Press, 2010), 21.

molecular units, whose precise arrangement was still variable enough to account for protoplasm's inherent complexity and the diversity of cellular types. A molecular diagram like the ones Schmidt created in Figure 5.17 showed how molecular theory was useful, as well as fundamental, for understanding biological structure. Having accepted Schmidt's images as a true reflection of nature, any other observer could see the patterns of birefringence under the polarized light microscope as affirming the molecular reality shown on the page. Ultimately, the colorful flashes of light seen under the polarized light microscope could never be interpreted without accepting the reality of the images on paper as an expression of the scientist's imagination of the biological microworld.

So lipid molecules and their orientation were in a way obvious to Schmidt, at least by 1939 or 1940 — and they were obvious to him in a rather different way than they were obvious to James Danielli in 1935, the latter guided by his deep education and work in physics and chemistry. Whether or not Wilhelm Schmidt "received" the exact ball and stick image of lipid structures from Harkins, McBain, or Lawrence does not matter as much as the various meanings and possibilities of molecular orientation and colloidal structure that were bound up in the ball and stick. Schmidt's use of this iconography was a clear departure from the epistemological standards of the communities that originally generated it: the physical chemists insisted first on the mathematical rigor of their theories, with images and molecular diagrams useful as only in pedagogy or as a heuristic. Schmidt and many biologists and biochemists who followed his example abandoned the physics and mathematics, embracing the images and other illustrations first and foremost as ways of expressing and thinking about a molecular reality. This departure transformed the idea of the molecule into an entity with both a clear physical identity and, crucially, an entity that could be stripped of much of the complex physics. This metaphysical distance between the physicalist abstraction of colloid chemistry and the realism of molecular biology can be seen easily by comparing Figure 3.6 to Figures 5.16 and 5.17 — the former an exceedingly rare illustration seen as having merely heuristic value, the latter two quite common and seen as essential to a scientific method. In physical chemistry and colloid chemistry,

not only had there been strong injunctions against structural determinacy at the molecular level, but any images they used were necessarily second class citizens: in physical and colloid chemistry, instrumental measurement and mathematical modeling were supposed to be the primary validation of a theory. In the biology of the cell and the search for the fine molecular structure of the protoplasm it was important to know the physics and chemistry, but it was just as important to be able to imagine and draw on paper the living molecular world.

Conclusion: Molecular Biology and the End of Protoplasm

Schmidt's diagram of the molecular structure of protoplasm came only towards the end of his 1939 address. The beginning consisted of a dense, detailed, and fast-paced review of the history of the cell, stretching back to Robert Hooke's observations of cork in 1667 and extending into Spencer and Haeckel's synthesis of continuity of cellular life with Darwin's theory of evolution. For Schmidt, the longer history of the cell and of cell theory pointed to a contemporary situation where "physics, chemistry, physiology, and morphology combine, thus fusing the study of the organism into a single unit."[1] The kind of molecular reasoning that Schmidt put on display in 1939 (Figure A) would have been familiar to experts in protoplasm research, but its most important role in the history of biology was as a demonstration broad audiences of biologists that molecular thinking was both possible and easy for those who were not so well versed in the details of physical chemistry. Strictly in terms of what individual theories were being brought together into his molecular conception of the cell, Schmidt in 1939 was not doing much beyond what Albert Frey-Wyssling had the year before in his monograph *The Sub-Microscopic Morphology of the Protoplasm and its Derivatives*. What was novel about the 1939 address was the broad audience of scientists to which it was pitched; for example, Schmidt's description of x-ray diffraction diagrams seems to have been written for those who had perhaps only heard that the technique existed. Much of the lecture was devoted to the most basic kinds of molecular and micellar structures in cells, and how they could be detected with polarization microscopy: chain molecules woven into fibers, fibers tangled into protein films (*Folien*), lipids forming layered lamellar structures. The image of the protoplasm was an eye-opening experience even to the very small number of experts in ultrastructure research, as Frey-Wyssling recalled after

1. W. J. Schmidt, "Der molekulare Bau der Zelle," *Nova Acta Leopoldina* 7 (1939): 1–24, on 7.

Schmidt's death. "Schmidt had finally summed up his treasure trove of experience with lamellar structures and membranes in a model of the ultrastructure of the cytoplasm," Frey-Wyssling wrote in 1975. "This image showed vacuoles, lipid droplets, and fat droplets embedded in a ground-plasma (*Grundplasma*) with polypeptide chains.…What is essential to me, however, is the surface-formation (*Behäutung*) of the vacuoles and lipid droplets. With this conception (*Auffassung*)," Frey-Wyssling added, "Schmidt anticipated today's theory of cellular compartmentalization with astonishing foresight."[2]

If biologists could speak of the material of living cells and organisms in terms of molecules and their organization, then was the idea that living cells and organisms were made of protoplasm (and its derivatives) redundant or unnecessary? Frey-Wyssling emphasized that this new molecular research was simply morphology at a very small scale — and through three different editions of his monograph, he kept the title *The Sub-Microscopic Morphology of the Protoplasm*, rather than changing it to "The Sub-Microscopic Morphology of the Cell." What had changed was more subtle than swapping the protoplasm and cell: it was now possible to talk about, draw, imagine, and otherwise think about molecules in living cells as individual *objects* — not substances, nor containers, but objects with their own identity, individuality, and agency. It was now possible in biology, perhaps even necessary, to describe the position, orientation, and spacing of individual molecules in larger organized systems. If Hugo von Mohl and Ferdinand Cohn had been moving the ontological basis of cell research away from object/entity thinking and towards an ontology of substances, then the kind of molecular thinking Schmidt and Frey-Wyssling embraced nearly a century later was arguably moving cell research back to thinking about objects — not membranes, or primordial utricles, but molecules.

2. Albert Frey-Wyssling, "The Scientific Work of W. J. Schmidt," *Microscopica Acta* 77, no. 2 (July 1975): 105–13.

This dissertation has shown, however, that this reversal from a substance-oriented ontology back to an object/entity-based ontology was potentially fraught endeavor: it relied on a kind of imaginative leap and the use of diagrams as both tools and representations of reality, forms of scientific reasoning that were and still are far from universally accepted. Biologists' arguments about the material basis of life were fundamentally shaped by questions and debates about both the nature of microscopic vision and the nature of matter itself. The enduring mystery about protoplasm was how a transparent, viscous substance could possess all of the qualities of life itself. A simplified, but not entirely inaccurate version of the history of protoplasm research might read: for a century, biologists explored that transparency and viscosity, all the while facing the challenge of how to see what was fundamentally invisible. The reconceptualization of protoplasm as a colloid in the early twentieth century was one answer to this conundrum — one compounded by serious doubts about fixation techniques — and colloid scientists essentially embraced protoplasm's transparency, rather than seeking to work around it. This dissertation has shown that biologists' molecularization of protoplasm happened through their introduction of new kinds of microscopic technique, and through their work to introduce new kinds of visual thinking to colloid science. The molecularization of biology and the molecularization of protoplasm did not come out of a conviction that colloid science was fundamentally wrong: it came out of refinements to and developments within colloid science, which included the theory of molecular orientation, the micellar theory of gel structure, and the application of polarized light microscopy to colloids via the Wiener's mixed body theory. The dominant history of molecular biology, which is focused on the biochemistry of individual types of molecules (DNA, hemoglobin, insulin, vitamins, etc.) and biological molecular mechanisms, has taken biologists' very notion of what a molecule *is* for

granted — and this history in turn has over-relied on the idea that colloid chemistry had to be overcome by macromolecular theory.[3]

The very idea that molecules (large and small) were important to think with came from biologists who grappled with and used colloid theory; until the 1920s biologists often and reasonably disagreed about what molecules *were*, and as a result they came to no consensus for how molecules might be important. This is not to say that the later repudiation of colloid chemistry (and micellar theory) was not genuine or historically important, but rather that the usual history of molecular biology *cum* biochemistry is only one story about the broader "molecularization" of biology.[4] For the rest of biology, molecules first had to become, ontologically, real; and, as chapter 5 especially shows, this could happen in large part through illustrations, rather than pure mathematical physics. Colloid chemistry had offered the only comprehensive physico-chemical theory of matter in the first half of the twentieth century, and the fundamental belief that the material basis of life is composed of molecules came from biologists' deep engagement with colloid physics. The idea that molecules were real and make up parts of larger cytological, cellular, and organismal systems — a biological-molecular world view, or what this dissertation has called a "biological microworld" — came from biologists' attempts to understand the physical, material, and even optical properties of protoplasm. The very conditions that allowed the molecular biological revolutions of the post-war period were created through biologists' deep engagement with colloid theory, and there would be no molecular

3. As a partial list: Robert C. Olby, "The Significance of the Macromolecules in the Historiography of Molecular Biology," *History and Philosophy of the Life Sciences* 1, no. 2 (1979): 185–98; Robert Olby, *The Path to the Double Helix* (Seattle: University of Washington Press, 1974); Soraya de Chadarevian and Harmke Kamminga, eds., *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*, Studies in the History of Science, Technology, and Medicine, v. 6 (Amsterdam: Harwood Academic Publishers, 1998); Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge: Harvard University Press, 1998), 12, 90–91, and 123.

4. For example, Angela Creager's history of how the physical chemist Edwin Cohn came to see purified blood serum fractions as different kinds of molecules appears to be atypical, requiring a theoretical engagement with the Debye-Hückel theory of electrolyte solutions that most biologists would not have been able to grapple with. Angela N. H. Creager, "Producing Molecular Therapeutics from Human Blood: Edwin Cohn's Wartime Enterprise," in *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*, ed. Soraya de Chadarevian and Harmke Kamminga (Amsterdam: Harwood Academic, 1998), 107–38.

biology without colloid chemistry. This was especially the case because so many biologists around and after the *fin-de-siècle* were exposed to physics and physicalist approaches to matter through colloid chemistry. What biologists abandoned in the 1930s was not colloid science as such, but rather the positivism and the descriptivist epistemology that had animated colloid science and many other areas of physics at the end of the nineteenth century.

At the same time, the elements of the protoplasm concept that had driven biologists to look for new physical and chemical ways of explaining its material and ontological foundations also drove a wedge between cell researchers. Biologists could choose to study protoplasm and the material basis of life; or they could choose to study the anatomy and objects within the cell, such as the nucleus, chromosomes, Golgi bodies, etc.; these kinds of cell anatomical objects were nearly irrelevant when talking about the protoplasm as such. Yet any time biologists broadened their discussions of protoplasm to move upward through the morphological hierarchy (Figures 4.7 and 4.15), cells and the objects within cells (that were presumably made of protoplasm) quickly entered into the conversation. As chapter 1 has shown, the ontological division between protoplasm-as-substance from cells (and organelles) as objects or containers was always partial, the cell and protoplasm concepts had considerable overlaps, and there had always been small inconsistencies and controversies over each term's precise definition. Complicating matters was the old definition by Hugo von Mohl and Ferdinand Cohn of protoplasm as the living *part* of the cell, distinguishable from the non-living cell wall, vacuoles, starch granules, etc. — an anatomical conception of protoplasm as an object that had no consistent form or boundary.

Even as he was making claims about and illustrating the molecular fine structure of the protoplasm, Schmidt disliked this lack of consistency within protoplasm theory. In the 1930s and '40s Schmidt liked to cite an obscure American journal article from 1925, whose author sent

questionnaires to every botanist he knew, asking them to define protoplasm, and specifically asking if the definition of "protoplasm" also encompassed the nucleus and other objects. He collected over sixty responses representing at least five different points of view. Thirty-eight of the sixty shared the view that protoplasm did, in fact, include the nucleus — a majority, but hardly an overwhelming scientific consensus. One of the thirty-eight, Johns Hopkins plant physiologist Burton Edward Livingston wanted to make sure people knew why he thought he was right, writing, "I don't care what protoplasm is so long as we know how it is built and how it operates." This breezy statement, tinged with the same positivism that pervaded colloid chemistry (*cf.,* Heilbrunn's "colloid chemists do not take the definition of their science too seriously"), was then followed with some glib philosophizing that illustrates how thinking about substance and composition in isolation from thinking about objects is possible, but problematic.[5]

> It seems foolish to try to define air, or soil, or protoplasm, or mince-meat, or plum-pudding, or chocolate fudge, or house-paint. When we attempt to define them we discover that there are many kinds of each, and that all of the constituents of any one mixture may be left out and replaced by different materials, without requiring the use of another general term. If a whole apple were found in the middle of the plum-pudding, we'd not call it a part of the pudding any more than if it were the baby's rubber doll that had been included by mistake. But if we took all of the dead grapes out of the plum-pudding, it wouldn't be a plum pudding any more! Apparently the distinction is based largely on size. Small pieces of apple are part of mince-meat, but larger pieces (fix your own limits of size) would be considered foreign bodies surrounded by mince meat.[6]

What evaded Livingston, and what seemed to evade almost biologist for about a century, was that language that was supposed to evoke a material substance could easily slip to evoke a material object. Alan Rocke has called this a "mental trick" hidden within both language and psychology, though Lakoff and Johnson might suggest that this "trick" is actually born of our mundane, everyday experience of materials as individuated objects, rather than as an abstract classification of substances.[7] Schmidt, for his part, hated the kind of reasoning that led to the protoplasm questionnaire to begin

5. See chapter 3, note 1.

6. Bruce Fink, "Some Considerations of Protoplasm," *Ohio Journal of Science* 25, no. 3 (1925): 99–113.

7. Alan J. Rocke, "Vinegar and Oil: Materials and Representation in Organic Chemistry," in *Objects of Chemical Inquiry*, ed. Ursula Klein and Carsten Reinhardt (Sagamore Beach: Science History Publications, 2014), 47–60;

with, calling it a "reminiscent of the old pseudo-problem of when a number of cereal grains can be said to form a 'heap' ('*Haufen*')."[8]

The power of protoplasm theory was never in its logical or metaphysical consistency, as much as that might have irritated Schmidt. Protoplasm was a central concept in modern biology because it posed a crucial problem that biologists felt they needed to address: What are living things made of? Along the way, crucial methodological, epistemological, visual, and perhaps even psychic prerogatives and problems transformed the way biologists answered that question. The historian of molecular biology Robert Olby had posed protoplasm and protoplasmically-oriented thinking as an historical puzzle, when writing about some comments the biochemist Joseph Needham had made about cells, protoplasm, and "living matter" in 1935:

> What is so strange about [Needham's] account of cell organisation is the complete absence of any reference to the organelles described by the cytologists and histochemists. Where are the mitochondria, known from 1865, named by [Carl] Benda in 1897, and isolated *en masse* by Robert Russell Bensley in 1934? What of the specialized zone of the cytoplasm which Garnier called the ergastoplasm in 1897, or microsomes of [Johannes] von Hanstein, and the much debated Golgi apparatus?[9]

This dissertation has shown why this might not have been so strange to Needham himself. By the 1930s the two different research agendas, driven by the cell on the one hand and protoplasm on the other, had diverged to such a point that they had become nearly incommensurable. Olby in 1986 correctly identified the reason for this lapse as being rooted in the history of early biophysics, which he argues "turned to physics for causal agents, engineering for models, and colloid science for simulations."[10] Yet behind this was a more profound issue than simply one of competing approaches to cellular structure or function: cytologists sought to show what objects were inside the cell, while

8. W. J. Schmidt, *Die Doppelbrechung von Karyoplasma, Zytoplasma, und Metaplasma*, 1–2.

9. Robert C. Olby, "Structural and Dynamical Explanations in the World of Neglected Dimensions," in *A History of Embryology*, ed. T. J. Horder, J. A. Witkowski, and C. C. Wylie (Cambridge: Cambridge University Press, 1986), 275–308, on 300. Olby is discussing Joseph Needham, *Order and Life*, Terry Lectures (New Haven: Yale University Press, 1936).

10. Robert C. Olby, "Structural and Dynamical Explanations in the World of Neglected Dimensions," 302.

the protoplasmologists sought to understand what substances cells were made of. When the answer to the latter problem moved towards “micelles” in the 1920s and “molecules” in the 1930s, it became possible to think of the cell as a container filled with tiny objects rather than as a tiny pouch of mixed fluids. The nineteenth century problem of protoplasm as living matter not only led biologists in the twentieth century to define what molecules meant to them, but it created a worldview that life was essentially, materially molecular.

Appendix: Birefringence, Polarized Light, and Polarized Light Microscopy

Polarized light microscopy is a method used to analyze birefringent materials, which have optically *anisotropy,* or generally oriented or directed patterns.. Polarization microscopy has been used for centuries in mineralogy as an essential aid in classification and identification of crystals, especially in samples that have a highly mixed composition (Figures AA to CC). A basic use of polarized light microscopy does not require much knowledge of the physics involved — *e.g.,* for determining the *sign of birefringence* — but most practitioners like W. J. Schmidt were well versed in the terminology and the broader implications of the physical theory. A polarizing microscope has the capacity to accept two polarizers, the polarizer below the condenser (Figure DD.1), and analyzer the above the objective (Figure DD.2); as well as a compensator, placed between the analyzer and the objective (Figure DD.3). All polarized light microscopes also have a graduated, rotating stage (Figure DD.4) that allows the specimen to be rotated around one, or sometimes two axes.

All polarization phenomena are fundamentally grounded in the wave theory of light, and have been recognized as such since Huygens tied *double refraction*, or *birefringence* to a vibratory theory of light in 1672; however, the modern interpretation was not developed until the late 1810s by Augustin Fresnel and François Arago.[1] Polarized light is light that vibrates only in a single plane (or only in a limited set of planes), perpendicular to the direction of the light ray (Figure EE.1), rather than in all planes perpendicular to the ray, as is the case with ordinary light (Figure EE.2). In much of the nineteenth century and up to the 1960s, the best optical device to produce polarized light was the Nicol prism, invented by William Nicol in 1828. The Nicol prism is a rhombohedral piece of Iceland spar with its faces cut at 68°, then cut diagonally in half, and then rejoined with

1. "Fresnel,Augustin," in *Complete Dictionary of Scientific Biography*, vol. 5 (Detroit: Charles Scribner's, 2008), 165–71.

Canada balsam (Figure FF).[2] Since the 1950s, inexpensive polymer Polaroid filters have been preferred, since they are more consistent, thinner, and allow for larger optical apertures and resolution. A ray of light coming through a Nicol prism or a Polaroid filter is linearly polarized in one direction.

In polarized light microscopy, two Nicol prisms — the polarizer and the analyzer — are "crossed", positioned so that their planes of polarization are perpendicular to each other (hence the phrase "between crossed Nicols"). Looking through the eyepiece at an empty stage, the observer will see darkness, since the analyzer has blocked out all of the light let through by the polarizer. However, if a *birefringent* specimen is placed on the stage, *i.e.,* a specimen that is itself capable of twisting and polarizing the vibration of light in some fashion, then the object will appear, illuminated against a dark background, and rendered in a shimmering rainbow of colors due to interference patterns the differing angles and intensities of the birefringent properties in the specimen under view.

More specifically, a birefringent material is one whose *refractive index* (*n*) is different depending on both the plane of polarization of light and the direction in which it is traveling.[3] The two extreme values of the material's refractive indices are n_e and n_o (sometimes labeled ε and ω), designating the refractive indices for the *extraordinary ray* (or *e-ray*) and the *ordinary ray* (or *o-ray*). The ordinary ray travels through the crystal obeying the normal laws of refraction, *i.e.* traveling at the same velocity in every direction of the crystal.[4] The extraordinary ray does not obey the normal laws of refraction: its velocity depends on the direction it is traveling and the plane of polarization.

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2. Leó Kristjánsson, *Iceland Spar and Its Influence on the Development of Science and Technology in the Period 1780–1930: Notes and References*, 4th ed. (Reykjavík: University of Iceland Institute of Earth Sciences, 2015), http://www.raunvis.hi.is/~leo/pdf/Iceland%20Spar_4%20utgafa_lowres.pdf.

3. The refractive index *n* for a given material is the ratio of the speed of light in a vacuum (*c*) to the speed of light in the material (*v*) so $n=c/v$ — thus any value of *n* means that light travels *n* times faster in a vacuum.

4. This would be Snell's law of refraction, $n_1 \sin\theta_1 = n_2 \sin\theta_2$, where θ_1 and θ_2 are the angles of incidence of the ray crossing the interface of the two media with refractive indices n_1 and n_2.

With the use of additional filters or compensators inserted between the analyzer and the eyepiece, the observer can determine whether the specimen is *negatively birefringent* or *positively birefringent*, and this sign of birefringence is used to classify minerals. In a negatively birefringent material, the ordinary ray travels more slowly than the extraordinary ray; rendered in terms of the refractive indices of the material, $n_e < n_o$. (Remember that n designates refractive index, so the higher value of n, the slower light is traveling.) In a positively birefringent material, the ordinary ray travels faster than the extraordinary ray, so $n_e > n_o$. More advanced, variable compensators can assist in quantitatively determining the strength of birefringence in a material, giving a numerical value for $\Delta n = n_e - n_o$.

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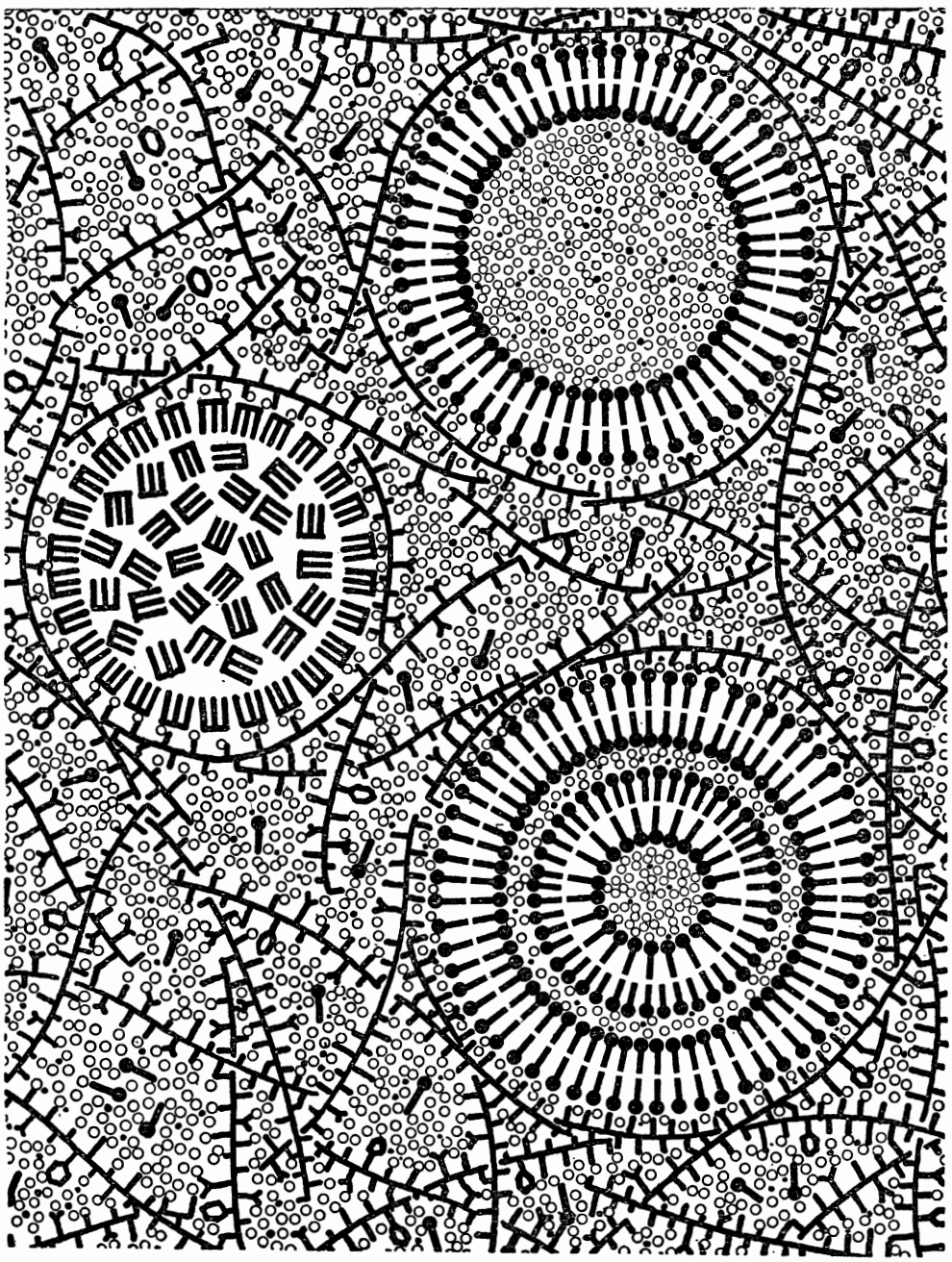


Abb. 8. Erläuterung des Feinbaues des Protoplasmas: ⊣⊣⊣ Protein-, •— Lipoid-, ⊏ Triglycerid-, ○ Wassermolekeln, ● Ionen. Oben eine Vakuole mit wässerigem Inhalt, umschlossen von einer bimolekularen Lipoidlamelle, in der Mitte links ein Öltropfen, unten ein Lipoidtropfen; dazwischen das Proteingerüst, das in seinen Maschen Wasser und andere Stoffe enthält.

Figure A. W. J. Schmidt's diagram of the fine structure of the protoplasm, prepared for the 1939 centenary celebration of cell theory. "Above a *vacuole* with watery contents, surrounded by a bimolecular lipid lamella, in the middle left an *oil drop*, below a *lipid drop*; in between the *protein framework*, which in its mesh contains water and other materials." W. J. Schmidt, "Der molekulare Bau der Zelle," *Nova Acta Leopoldina* 7 (1939): 1–24, on 17.

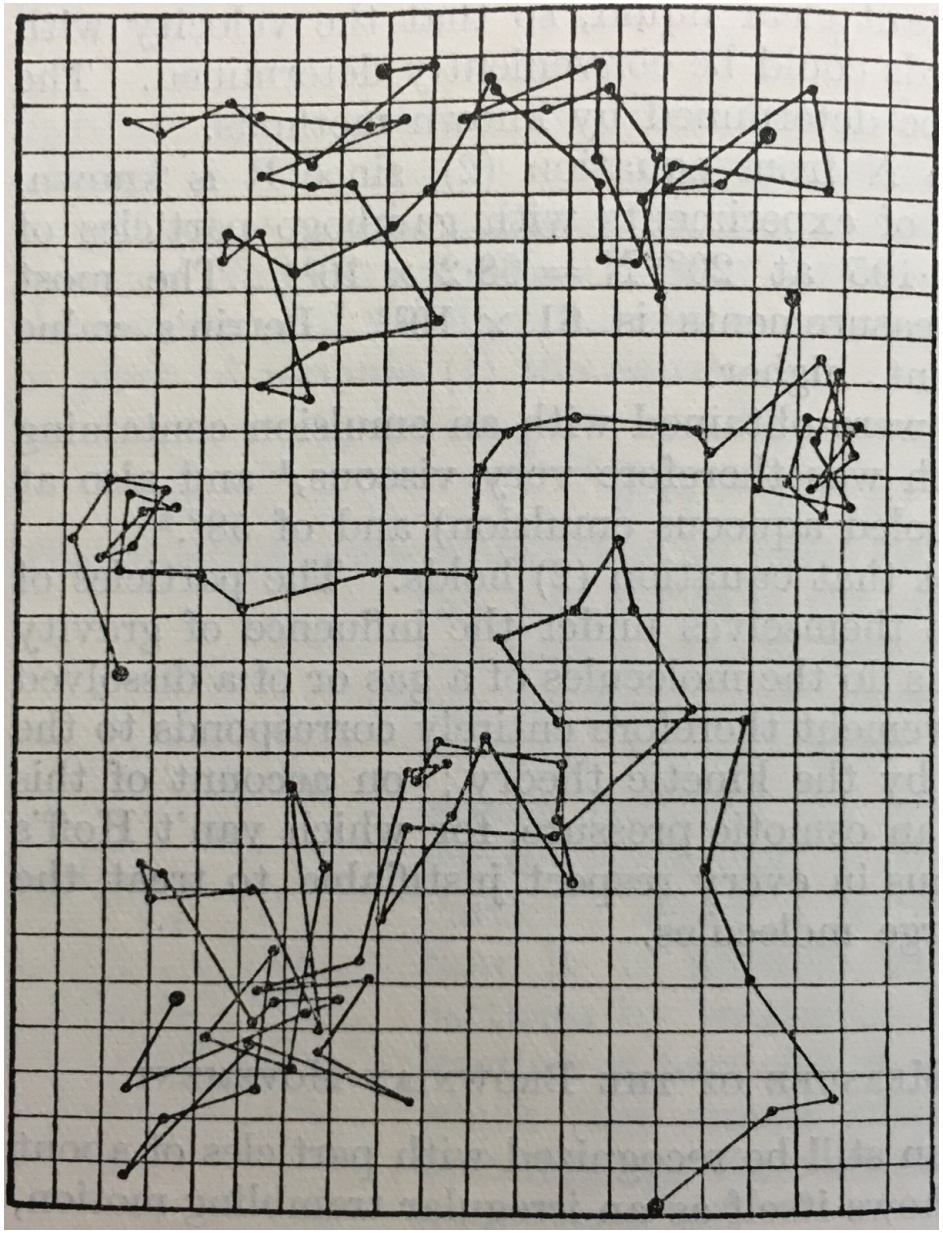


Figure B. Jean Perrin's 1909 figure of Brownian movement. Originally in "Mouvement brownien et realité moléculaire," *Annales de chimie et de physique* ser. 8, 18 (1909): 5–114. (This reproduction is from Herbert Freundlich, *Colloid & Capillary Chemistry*, trans. H. Stafford Hatfield [London: Methuen & co., 1926], 346.)

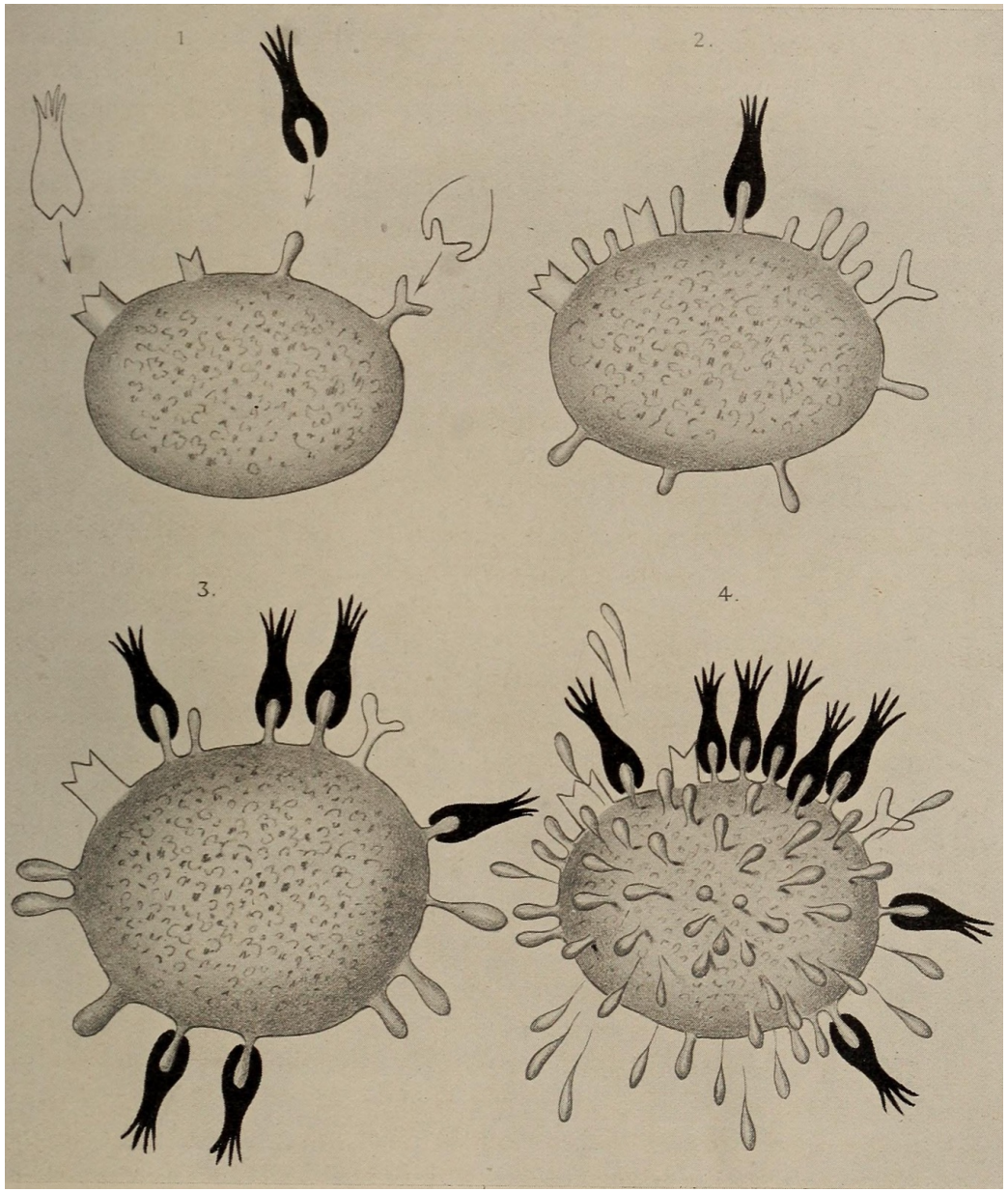


Figure C. Paul Ehrlich referred to these figures as "purely arbitrary diagrams" of his side-chain theory that "must be regarded quite apart from all morphological considerations, and as being merely a pictorial method of presenting my views on cellular metabolism, and the method of toxine action and antitoxine formation during the process of immunisation." Nevertheless, as Cambrosio, Jacobi, and Keating show, Ehrlich and other immunologists made good use of these images to categorize and classify pharmaceuticals, antitoxins, and immune reactions.

From Paul Ehrlich, "Croonian Lecture: On Immunity with Special Reference to Cell Life," *Proceedings of the Royal Society of London* 66 (1899): 424–48.

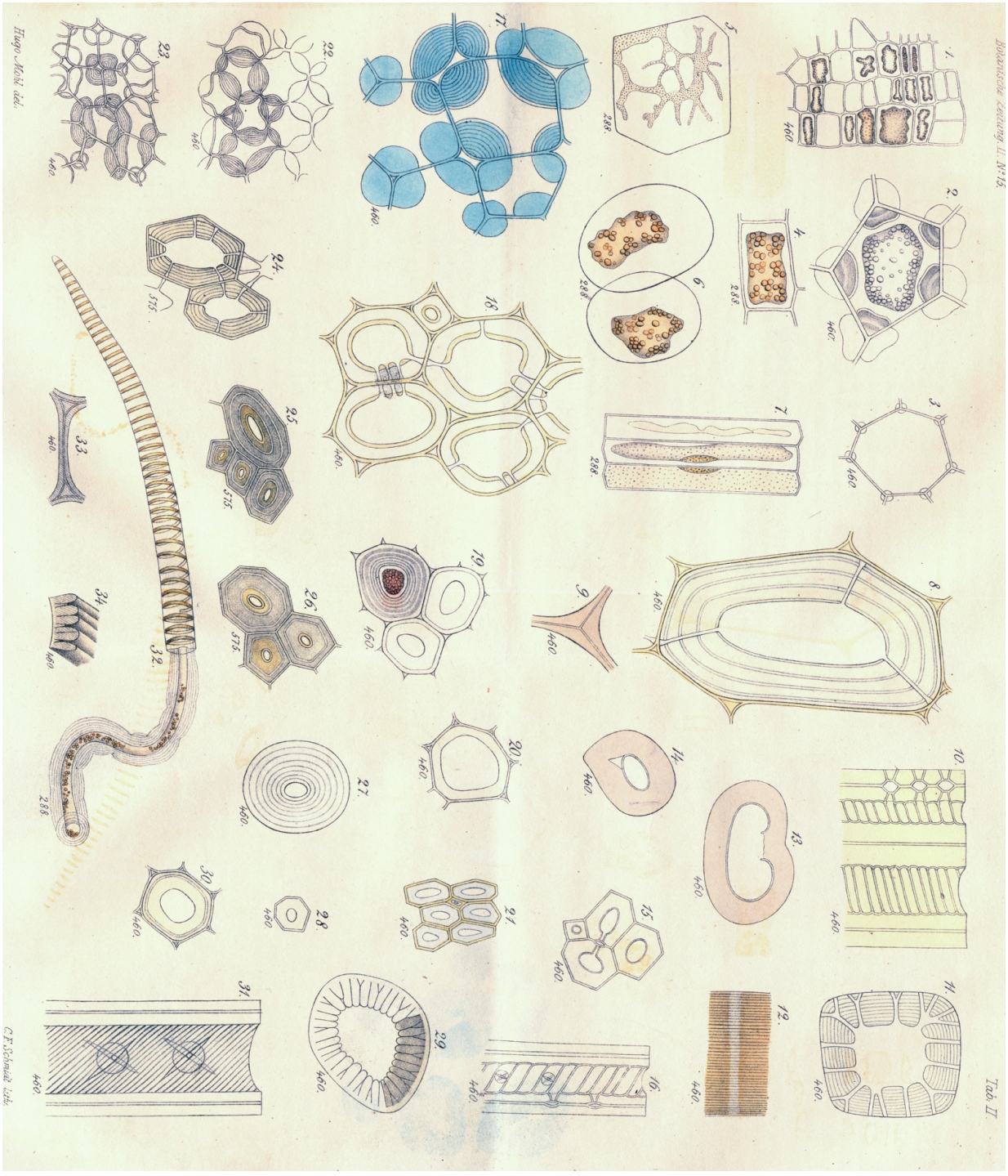


Figure 1.1: Hugo von Mohl's schematic illustrations of the *Primordialschlauch*. This is the whole plate from Hugo von Mohl, "Einige Bemerkungen über den Bau der vegetabilischen Zelle," *Botanische Zeitung* 2, nos. 15–19 (1844): 273–77, 289–94, 305–10, 321–26, 337–42.

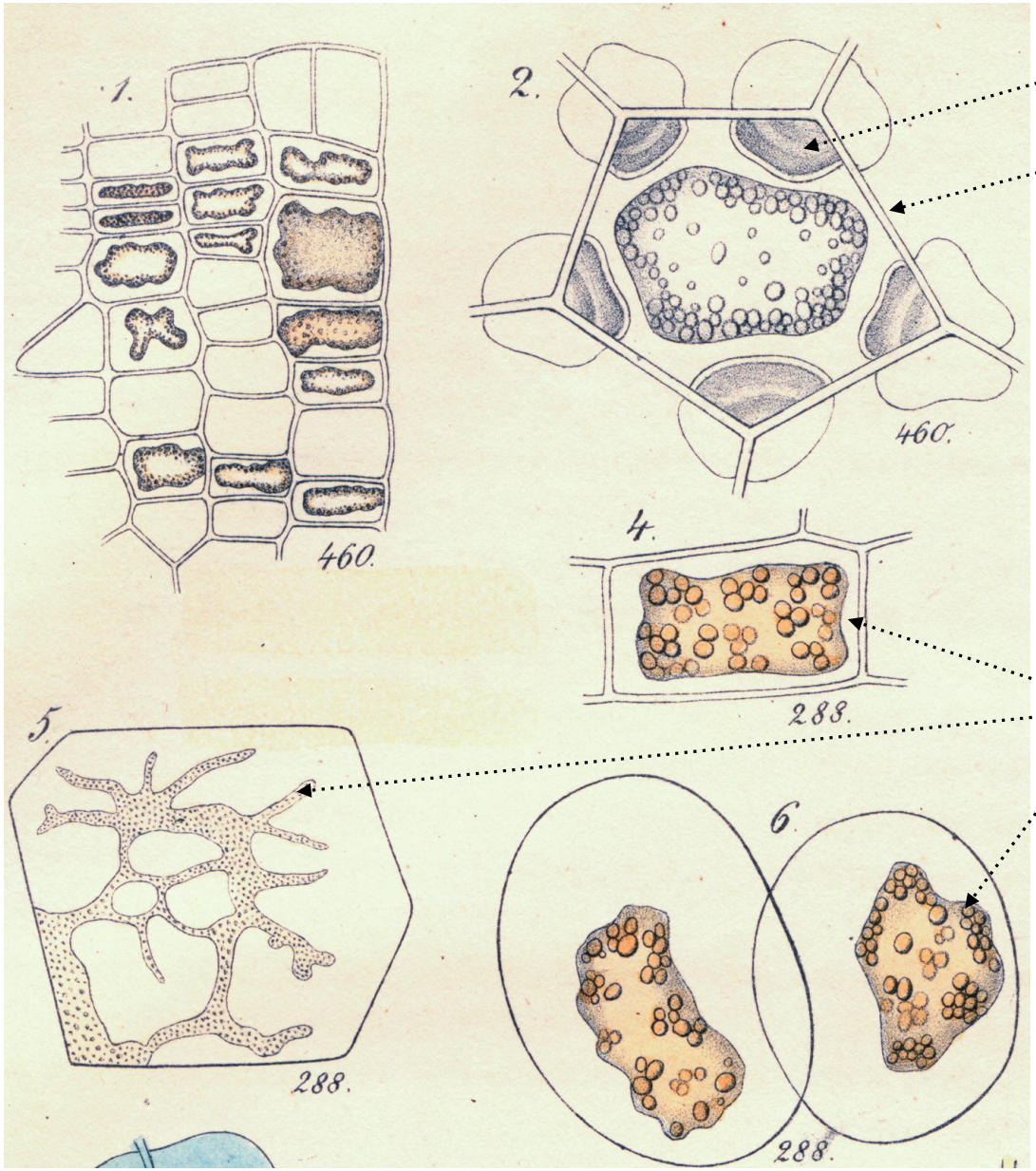
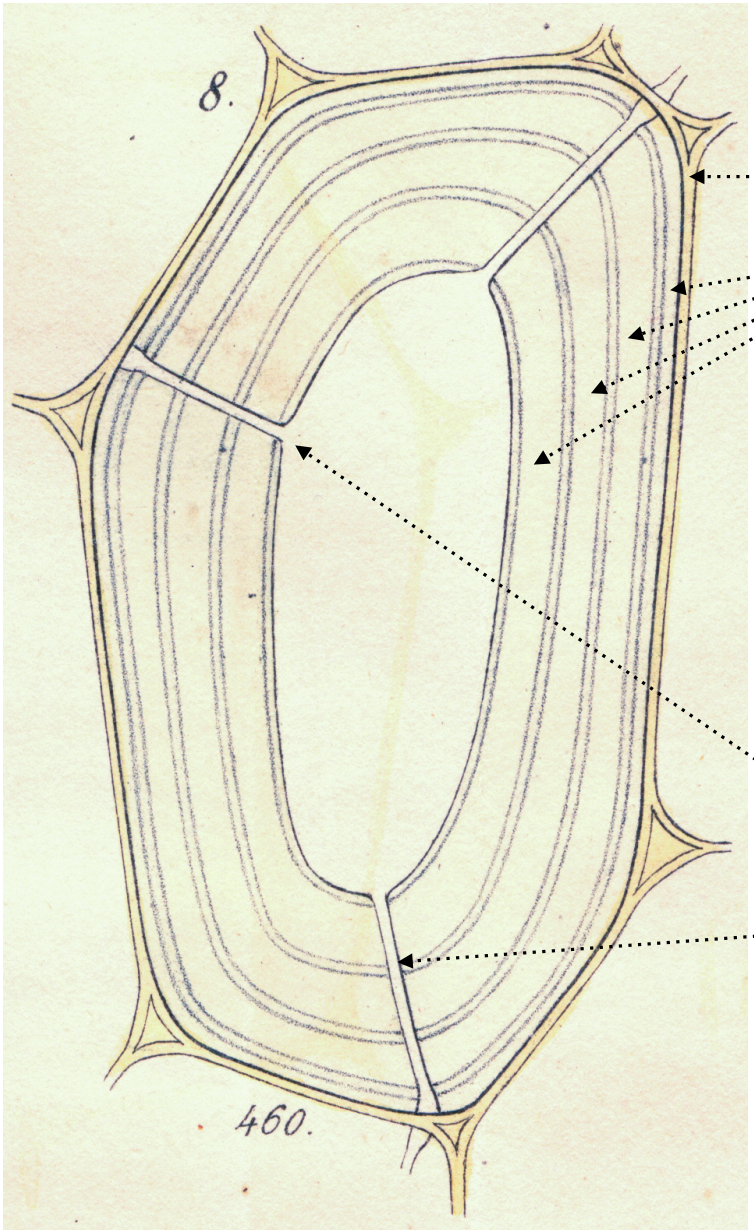


Figure 1.2: Detail from Fig. 1.1. These show the complete separation of the primordial utricle from the outermost, primary membrane. Von Mohl's Fig. 2 also shows the arched curve of the "secondary" membranes, which he understood as the "mechanical" result of how the primordial utricle grew the cell. His Fig. 5 shows the primordial utricle still partially adhered to the cell wall.

Hugo von Mohl, "Einige Bemerkungen über den Bau der vegetabilischen Zelle," *Botanische Zeitung* 2, nos. 15–19 (1844): 273–77, 289–94, 305–10, 321–26, 337–42.



primary membrane

layers of the “secondary membrane”

“Porenkanäle”

Figure 1.3: Detail from Fig. 1.1. Bast fiber cell, stained with iodine. Rather than show the “arched curve” of segments of the secondary membranes, this figure highlights what von Mohl refers to alternately as the *“Porenkanäle”* (pore-canals) or *“Tüpfelkanäle”* (canals of dots, confusingly) in the secondary membrane, through which the primordial utrical remains attached to the primary membrane.

Hugo von Mohl, “Einige Bemerkungen über den Bau der vegetabilischen Zelle,” *Botanische Zeitung* 2, nos. 15–19 (1844): 273–77, 289–94, 305–10, 321–26, 337–42.

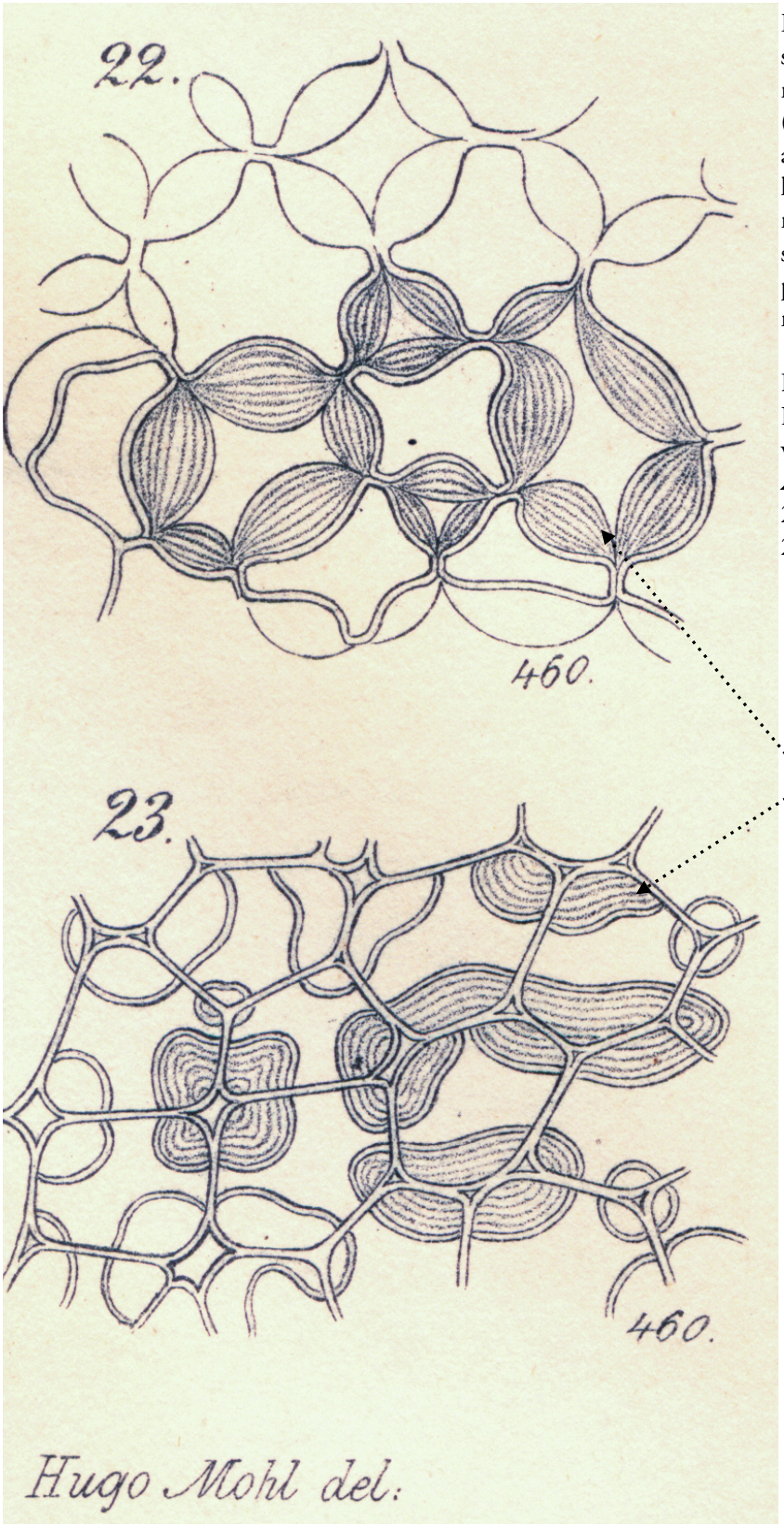


Figure 1.4: Detail from Fig. 1.1, showing the layered secondary membranes before (22) and after (23) fixation with hydrochloric acid. For von Mohl, the way the layers retreat into "curved arches" rather than as concentric circles shows the attachment of the primordial utricle to the primary membrane.

Hugo von Mohl, "Einige Bemerkungen über den Bau der vegetabilischen Zelle," *Botanische Zeitung* 2, nos. 15–19 (1844): 273–77, 289–94, 305–10, 321–26, 337–42, on 341.

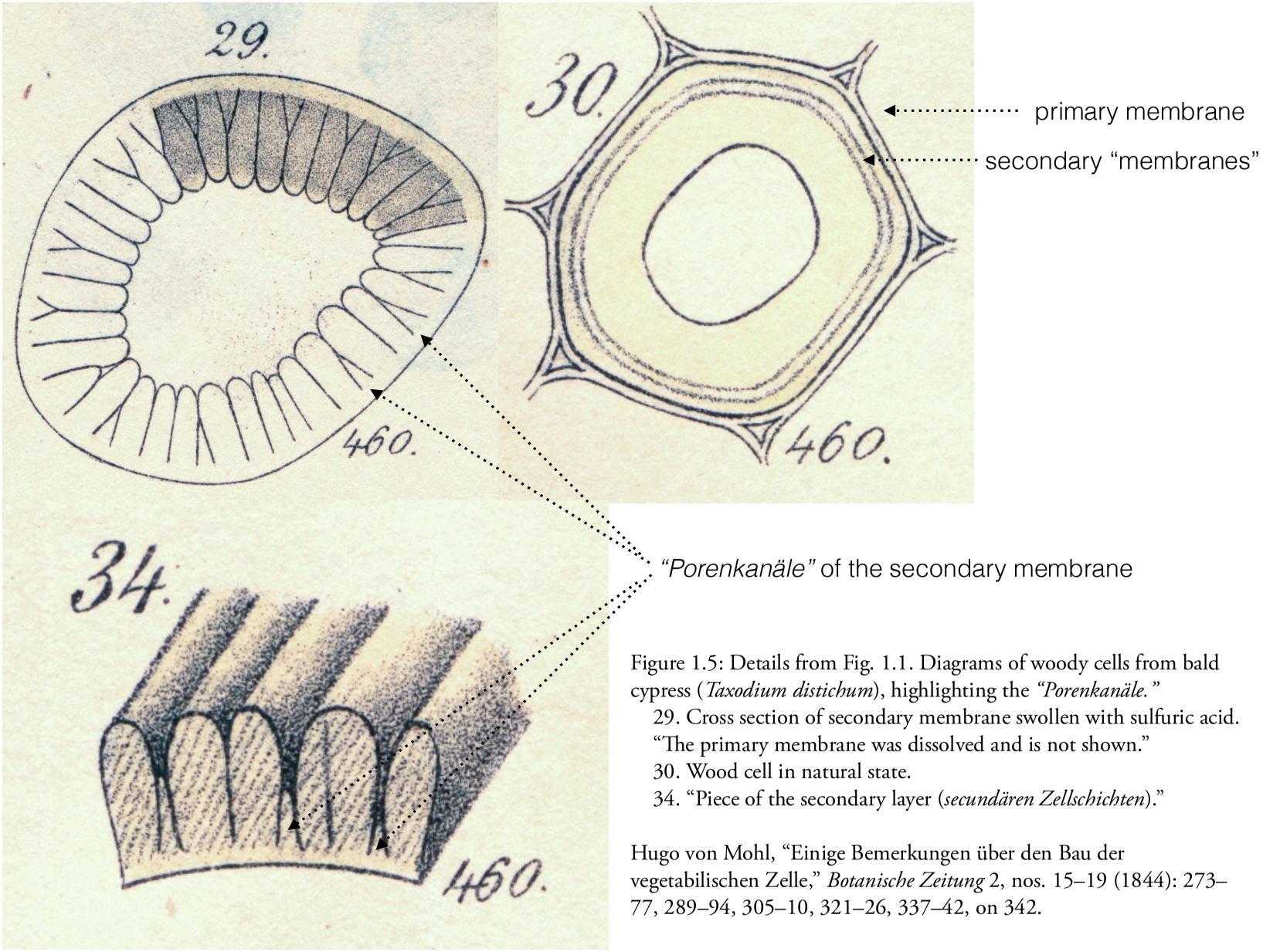


Figure 1.5: Details from Fig. 1.1. Diagrams of woody cells from bald cypress (*Taxodium distichum*), highlighting the *"Porenkanäle."*

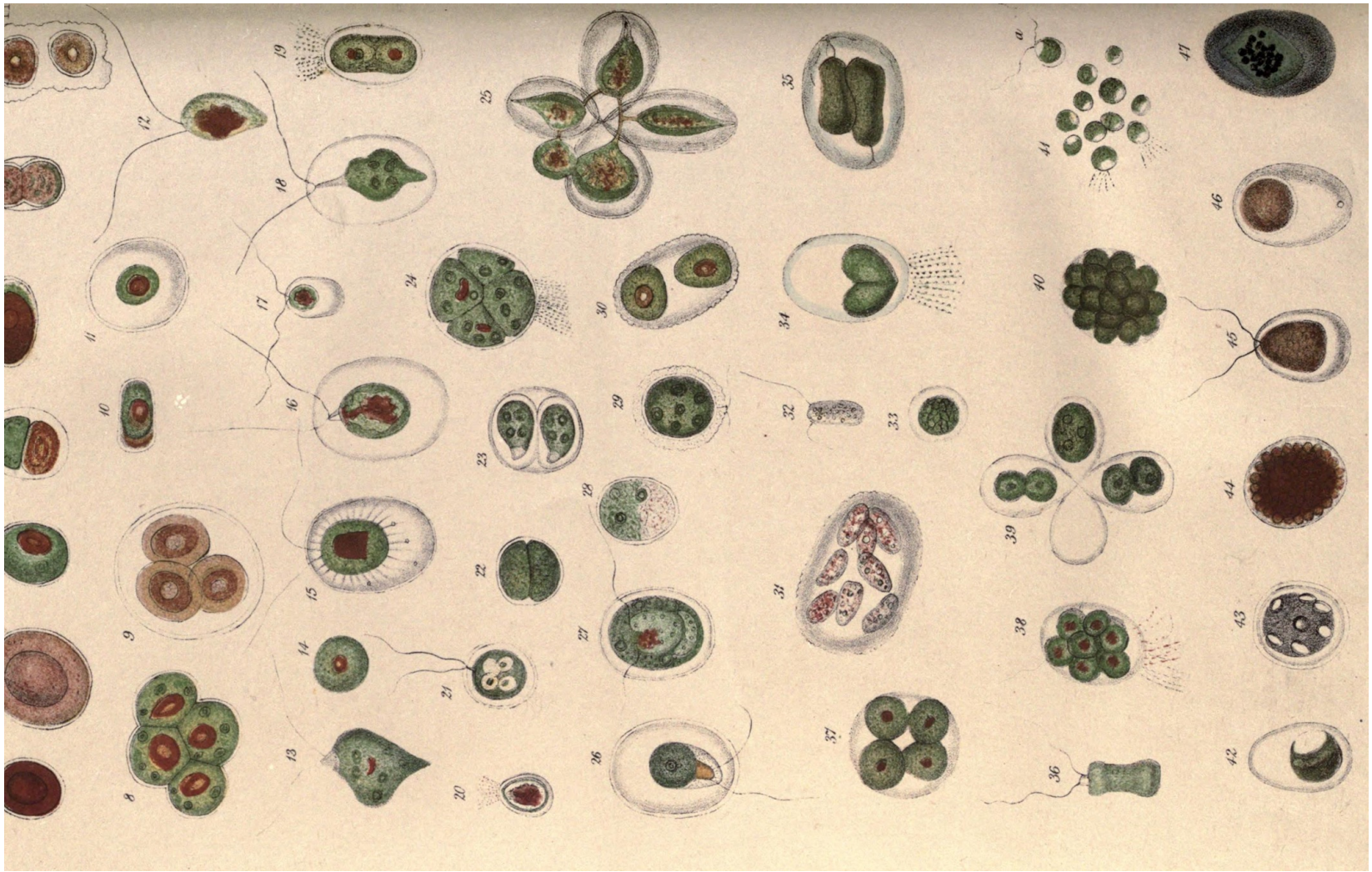
29. Cross section of secondary membrane swollen with sulfuric acid. "The primary membrane was dissolved and is not shown."

30. Wood cell in natural state.

34. "Piece of the secondary layer (*secundären Zellschichten*)."

Hugo von Mohl, "Einige Bemerkungen über den Bau der vegetabilischen Zelle," *Botanische Zeitung* 2, nos. 15–19 (1844): 273–77, 289–94, 305–10, 321–26, 337–42, on 342.

Figure 1.6: Ferdinand Cohn's study of *Protococcus pluvialis*. This is the abbreviated plate from Ferdinand Cohn, "On the Natural History of Protococcus Pluvialis," trans. George Busk, *Botanical and Physiological Memoirs of the Ray Society* 10, no. 2 (1853): 517–64.



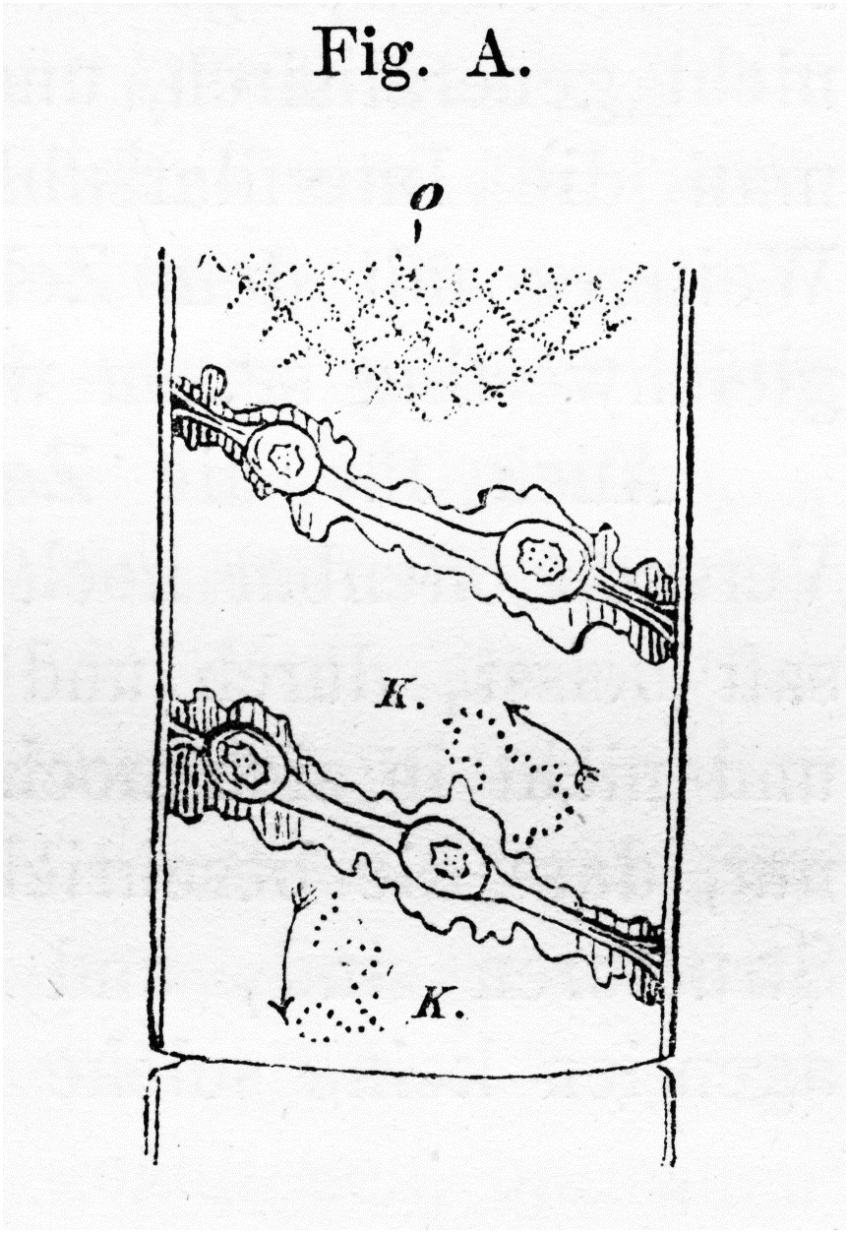


Figure 2.1. Walther Flemming's schematic representation of a *Spirogyra* cell fixed in 1–2% osmic acid fluid. *"O"* indicates the net-shaped coagulation, the product of osmium fixation. The dotted lines *"K"* mark the path of the Brownian motion (*"Molecularbewegung"*) of what Flemming called the "dancing granules." Flemming argued that, "If the osmium net were preformed in life, then it would not allow this free dance, so it must be a clot (*Gerinnung*)."

Walther Flemming, *Zellsubstanz, Kern und Zelltheilung* (Leipzig: F. C. W. Vogel, 1882), 51.

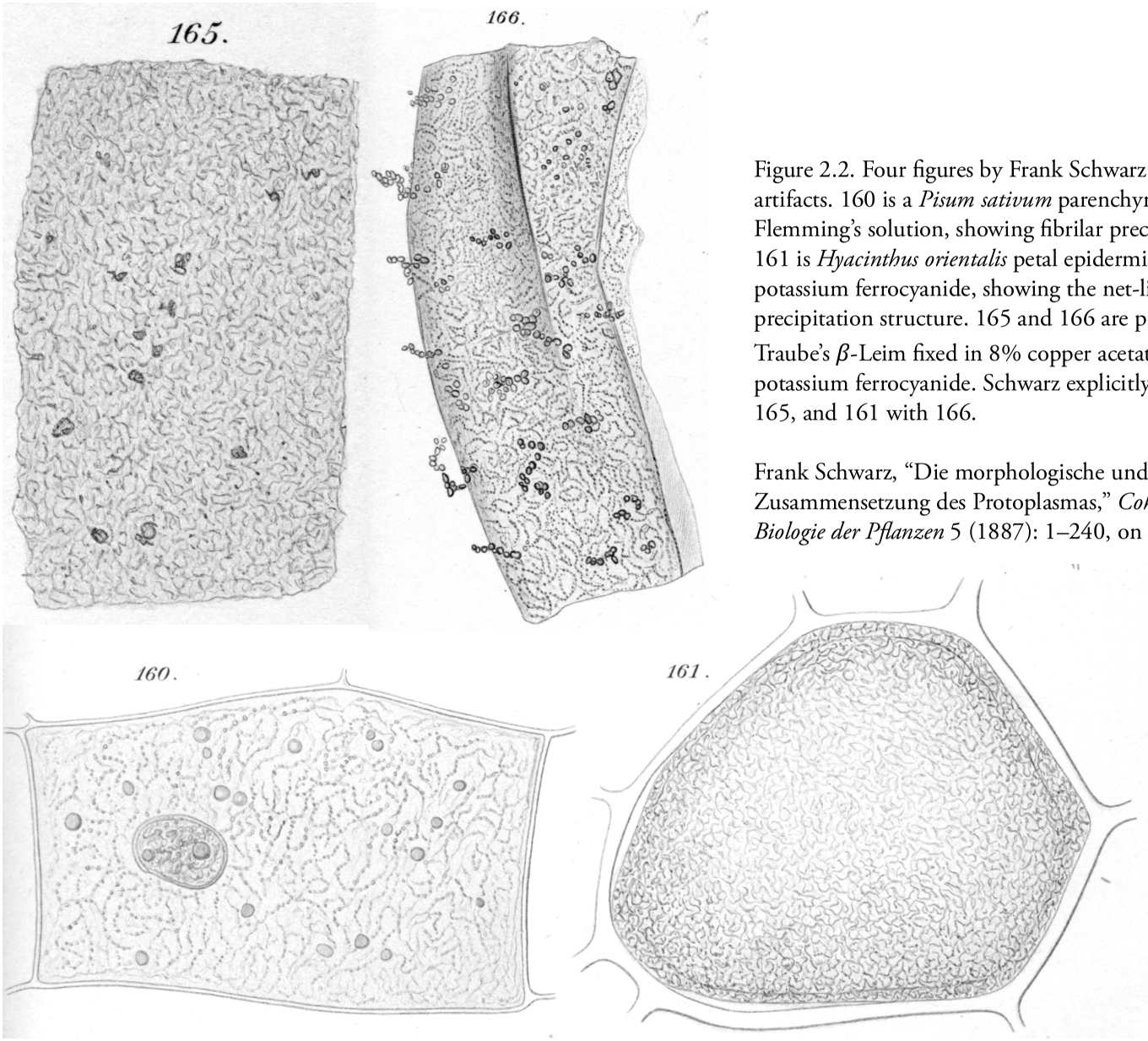


Figure 2.2. Four figures by Frank Schwarz showing fixation artifacts. 160 is a *Pisum sativum* parenchyma cell fixed with Flemming's solution, showing fibrilar precipitation (720x); 161 is *Hyacinthus orientalis* petal epidermis fixed with acetic-potassium ferrocyanide, showing the net-like fibrillar precipitation structure. 165 and 166 are precipitations of Traube's β-Leim fixed in 8% copper acetate and 10% acetic-potassium ferrocyanide. Schwarz explicitly compared 160 with 165, and 161 with 166.

Frank Schwarz, "Die morphologische und chemische Zusammensetzung des Protoplasmas," *Cohns Beiträge zur Biologie der Pflanzen* 5 (1887): 1–240, on 148

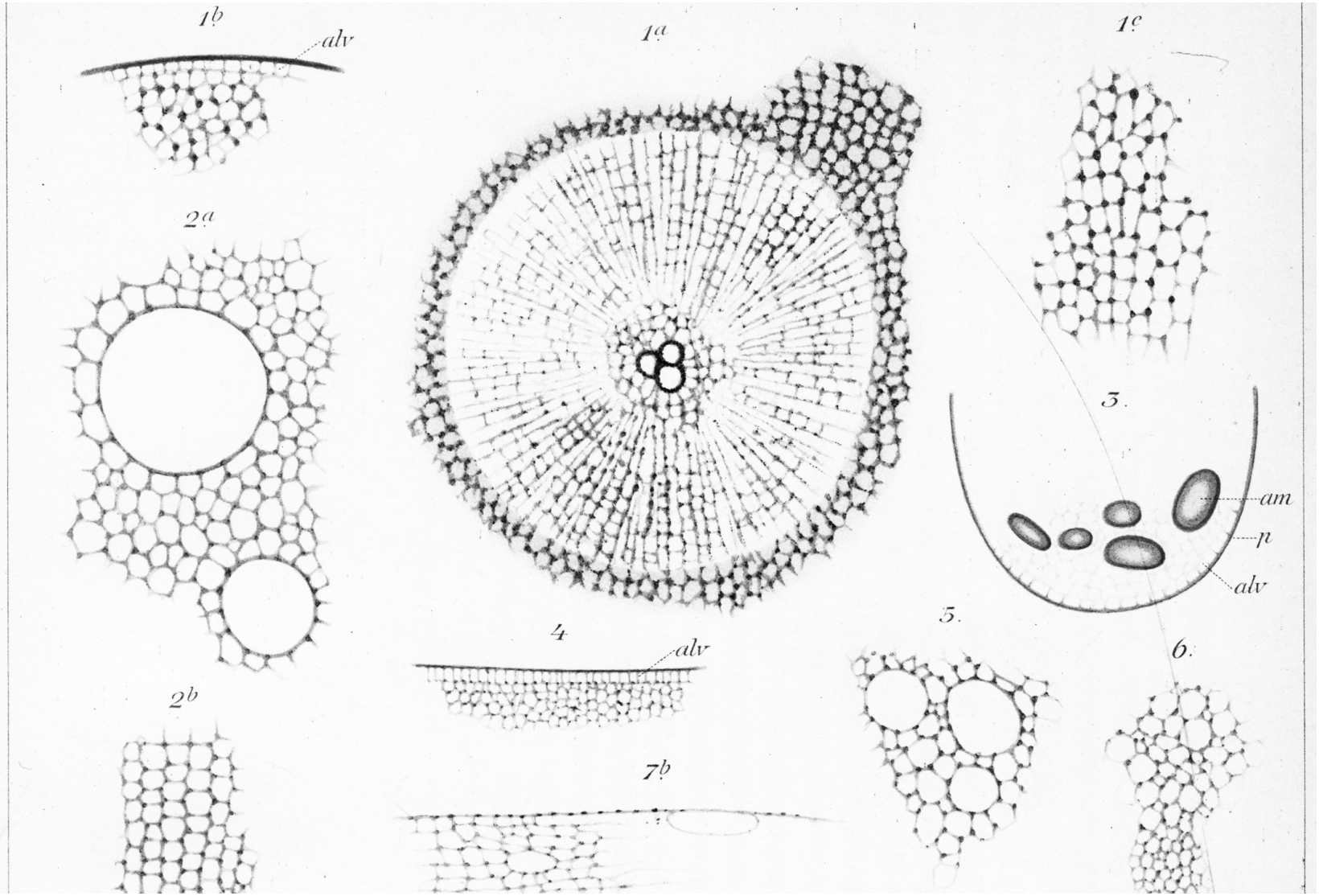


Figure 2.3. Otto Bütschli's olive oil foams, items 4–7, 1200x. Item 1, a–c show the protoplasm of a sea urchin egg for comparison; 2 and 3 show the protoplasm of two different protozoa, fixed with osmic acid. This is the upper half of Plate 3, Otto Bütschli, *Untersuchungen über mikroskopische Schäume und das Protoplasma* (Leipzig: Wilhelm Engelmann, 1892).

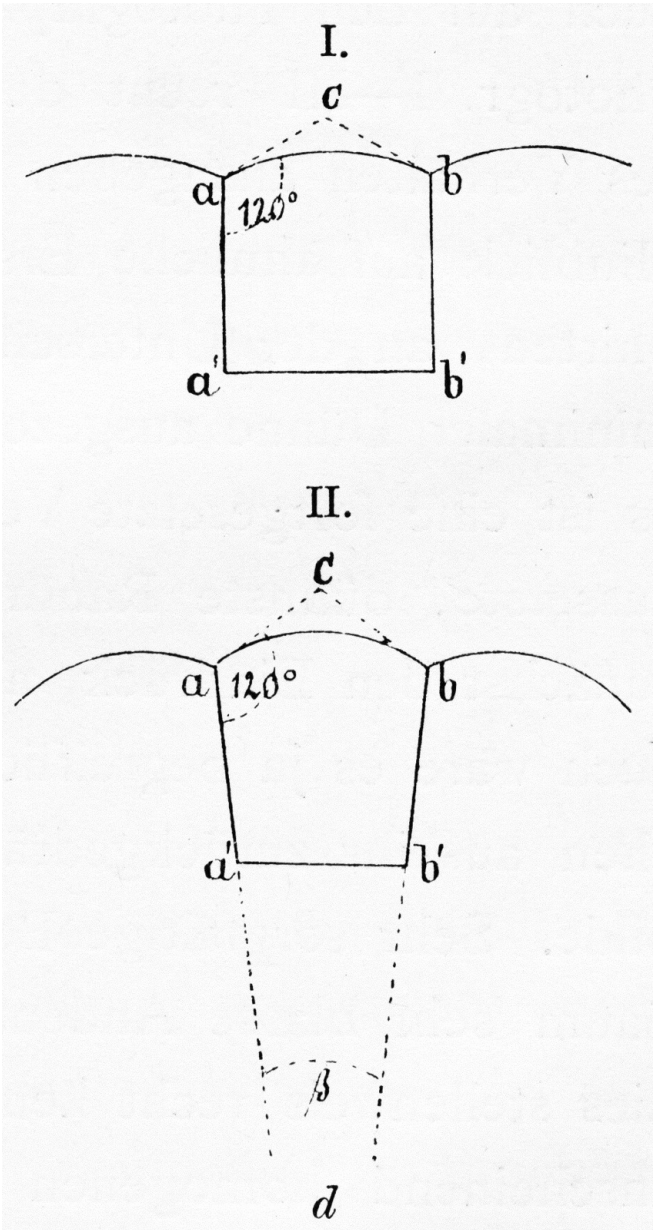
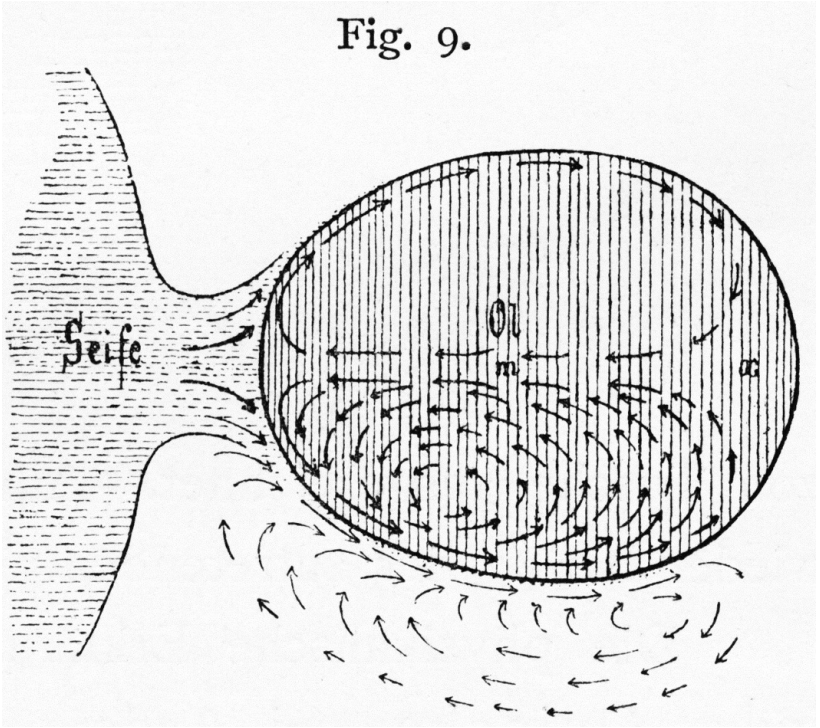


Figure 2.4. Two of figures describing the structure and behavior of olive oil foams. Left: Bütschli's attempt at a geometrical explanation the surface of an olive oil foam. Below: Bütschli's hypothesis for protoplasmic streaming, by demonstration of soap solution with india ink, in contact with a drop of olive oil foam frothed with lamp-black. The arrows indicate the "system of radiating currents" created by the surface contact between soap and oil. Otto Bütschli, *Untersuchungen über mikroskopische Schäume und das Protoplasma*. (Leipzig: Wilhelm Engelmann, 1892), 25, 43



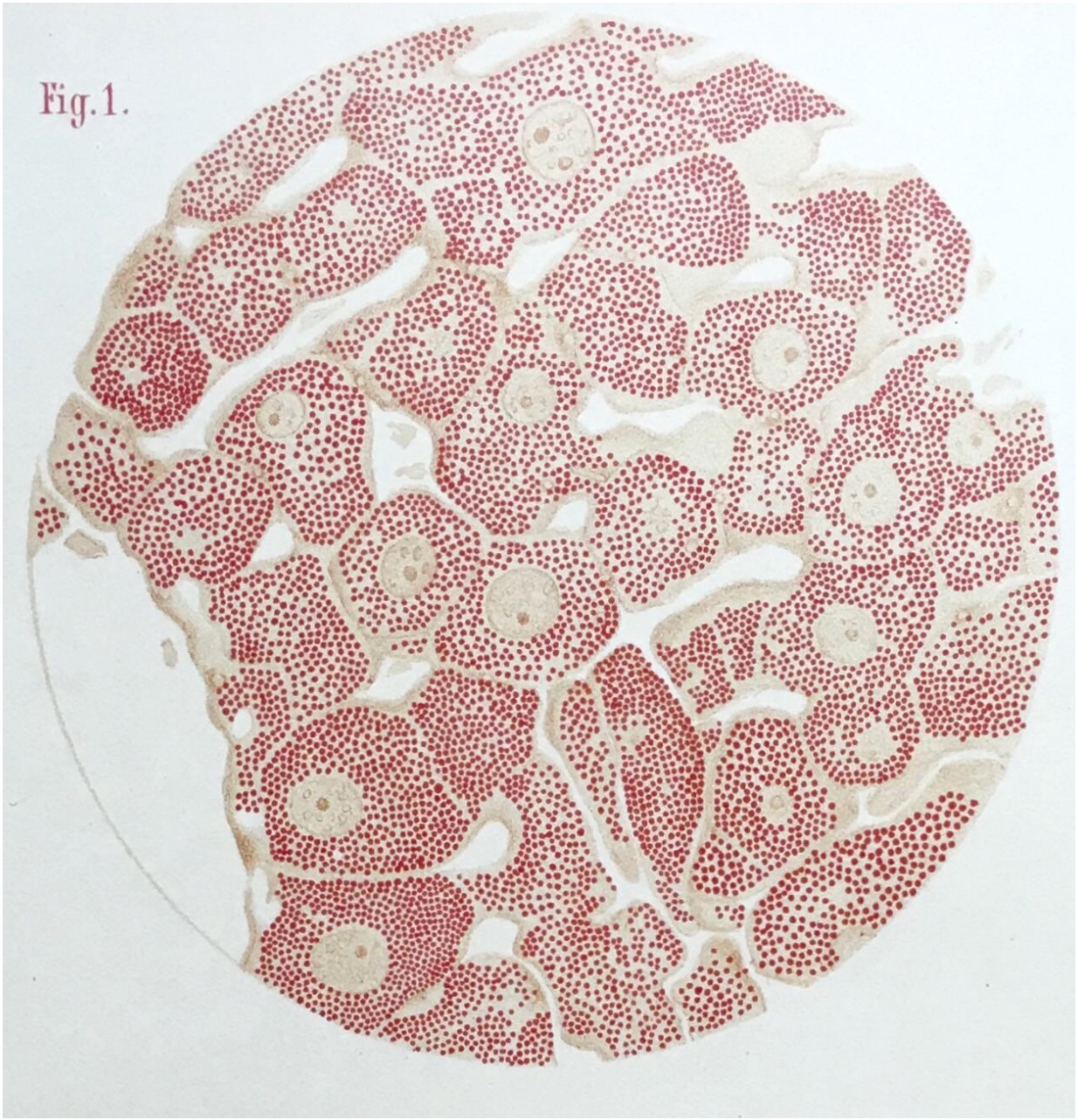


Figure 2.5. Altmann's granular "elementary organisms," shown in mouse liver cells fixed with osmium mixture, 700x. Plate II.A. from Richard Altmann, *Die Elementarorganismen und ihre Beziehungen zu den Zellen* (Leipzig: Veit & comp., 1890).

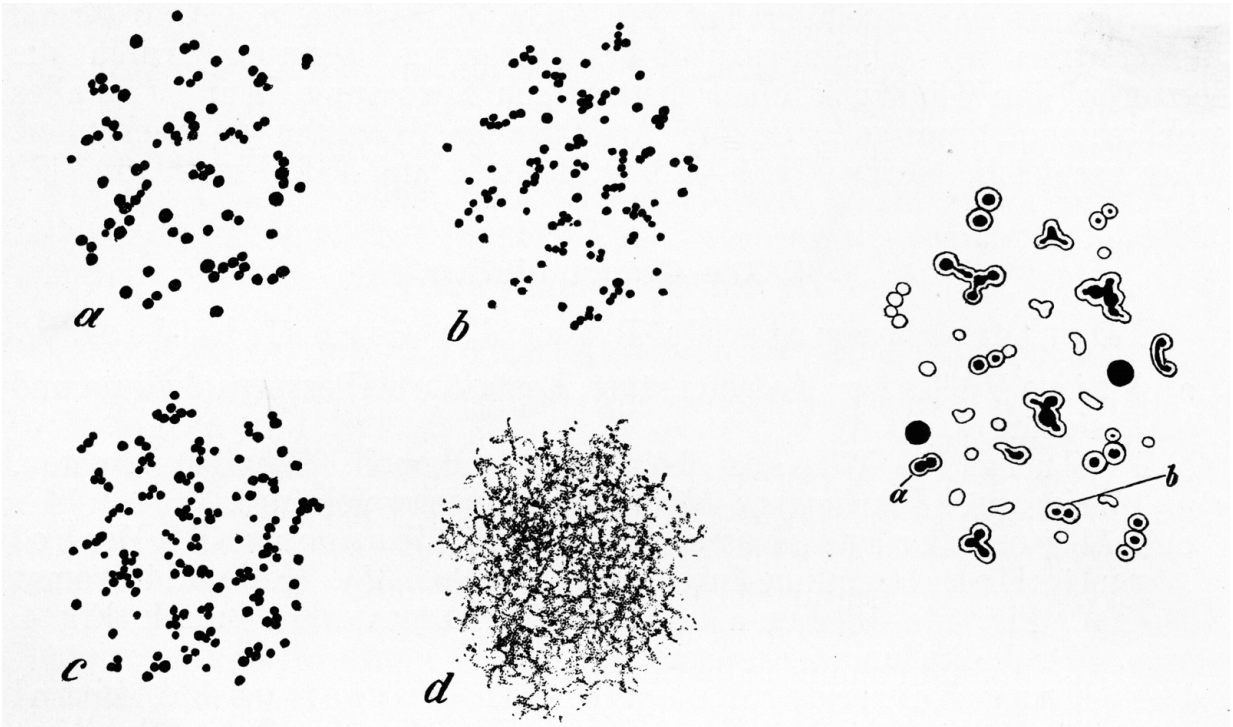


Fig. 1. Fig. 2.

Fig. 1. Fällung einer deutlich alkalischen Albumoselösung, 5-proc., in 0,2 Proc. KOH mit *a* 1-proc. Platinchlorid, *b* FLEMMING'scher Lösung, *c* 0,5-proc. Chromsäure, *d* ALTMANN'S Gemisch. Die „sauren" Fixirungsmittel (Fig. *a*—*c*), der Gruppe d angehörig, geben auch bei alkalischer Reaktion schnell typische Granula, während ALTMANN'S Gemisch sehr langsam unbedeutende Gerinnsel fällt. Man vergleiche dazu Fig. 4. (Vergr. 600.)

Fig. 2. Albumose, 20-proc., eben sauer mit conc. wässrigem Sublimat gefällt, mit Eisenhämatoxylin gefärbt und auf Spiegel differenzirt. Man beachte die verschiedenen Verschmelzungsformen der zunächst gefällten Globuliten, woraus sich dann auch Theilungs- und Zwillingsbilder (*a* und *b*) ergeben. (Vergr. 1500.)

Figure 2.6. "Granular" (*a–c*) and "clotted" (*d, "Gerinnseln"*) precipitates of protein solution.

a. Fixed with platinum chloride
b. Fixed with Flemming's solution
c. Fixed with 0.5% chromic acid
d. Fixed slowly with Altmann's mixture

Alfred Fischer, *Fixirung, Färbung und Bau des Protoplasmas: Kritische Untersuchungen über Technik und Theorie in der neueren Zellforschung* (Jena: Fischer, 1899), 34.

Figure 2.7: Varieties of clotted and granular precipitates from Fischer's ten different mixtures of protein solutions, fixed and stained. Alfred Fischer, *Fixirung, Färbung und Bau des Protoplasmas* (Jena: Fischer, 1899).

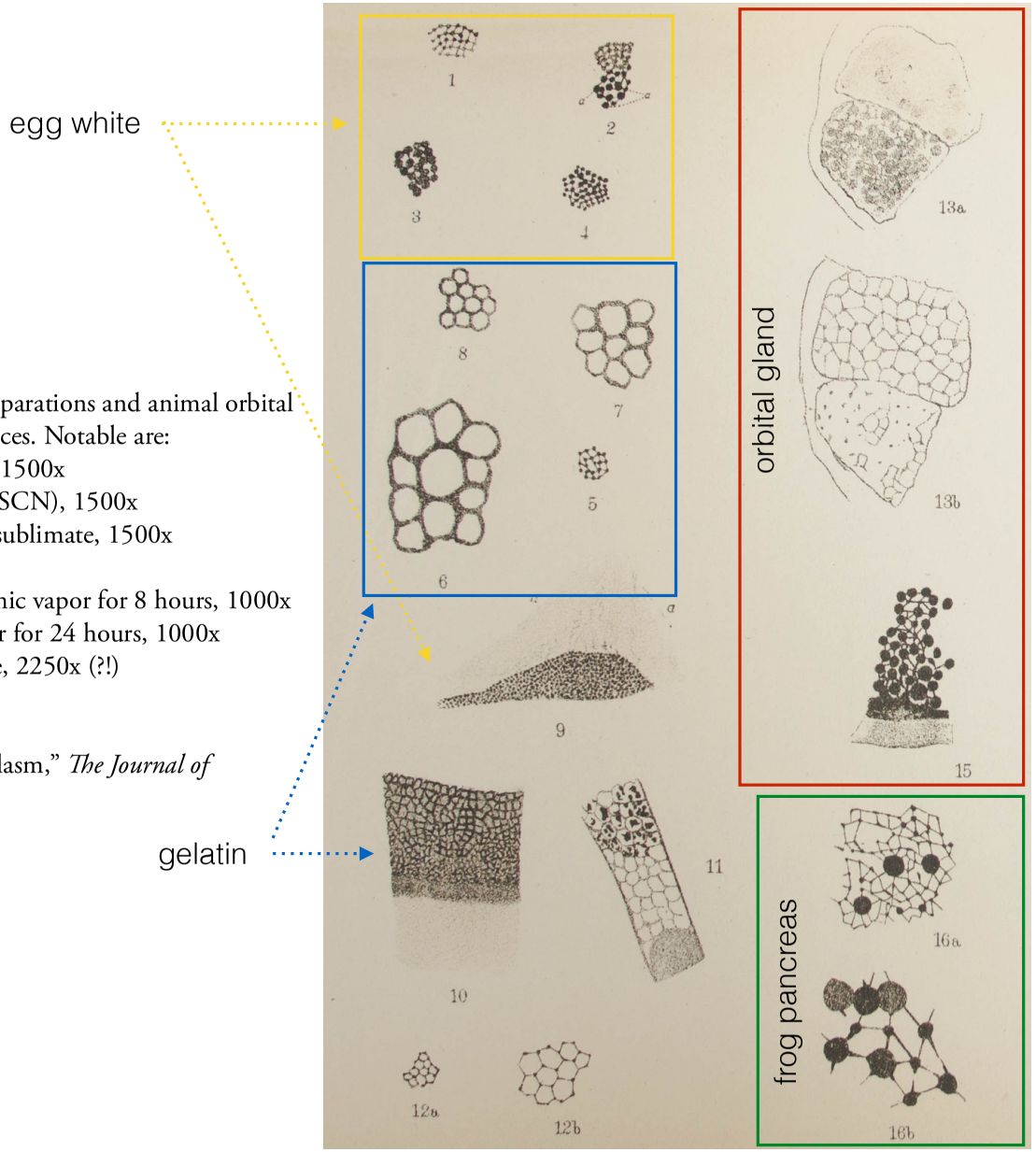


Figure 2.8: Hardy's images of fixed artificial preparations and animal orbital gland cells, showing their very similar appearances. Notable are:

1–3: 13, 30, and 60% egg white, sublimate, 1500x
4: 13% egg white, potassium thiocyanate (KSCN), 1500x
5–8: 3, 10, 25, and 50% gelatin, fixed with sublimate, 1500x
9: egg white "fixed" by steam cooking, 450x
13, a and b: kitten orbital gland, fixed in osmic vapor for 8 hours, 1000x
15: puppy orbital gland, fixed in osmic vapor for 24 hours, 1000x
16, a and b: frog pancreas, fixed in sublimate, 2250x (?!)

W. B. Hardy, "On the Structure of Cell Protoplasm," *The Journal of Physiology* 24, no. 2 (May 11, 1899): 158–210.

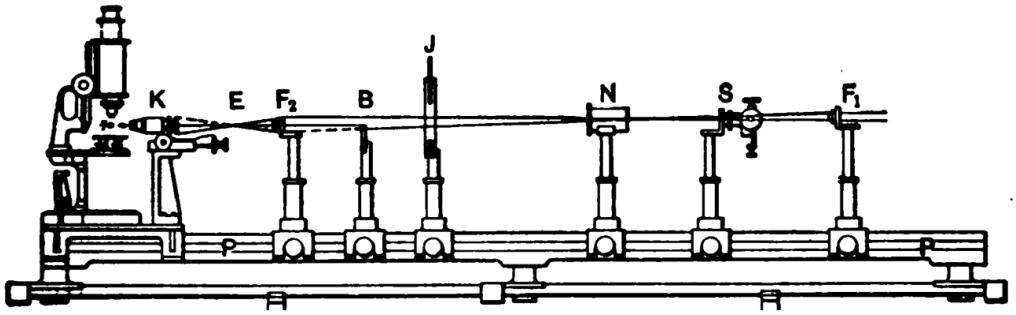
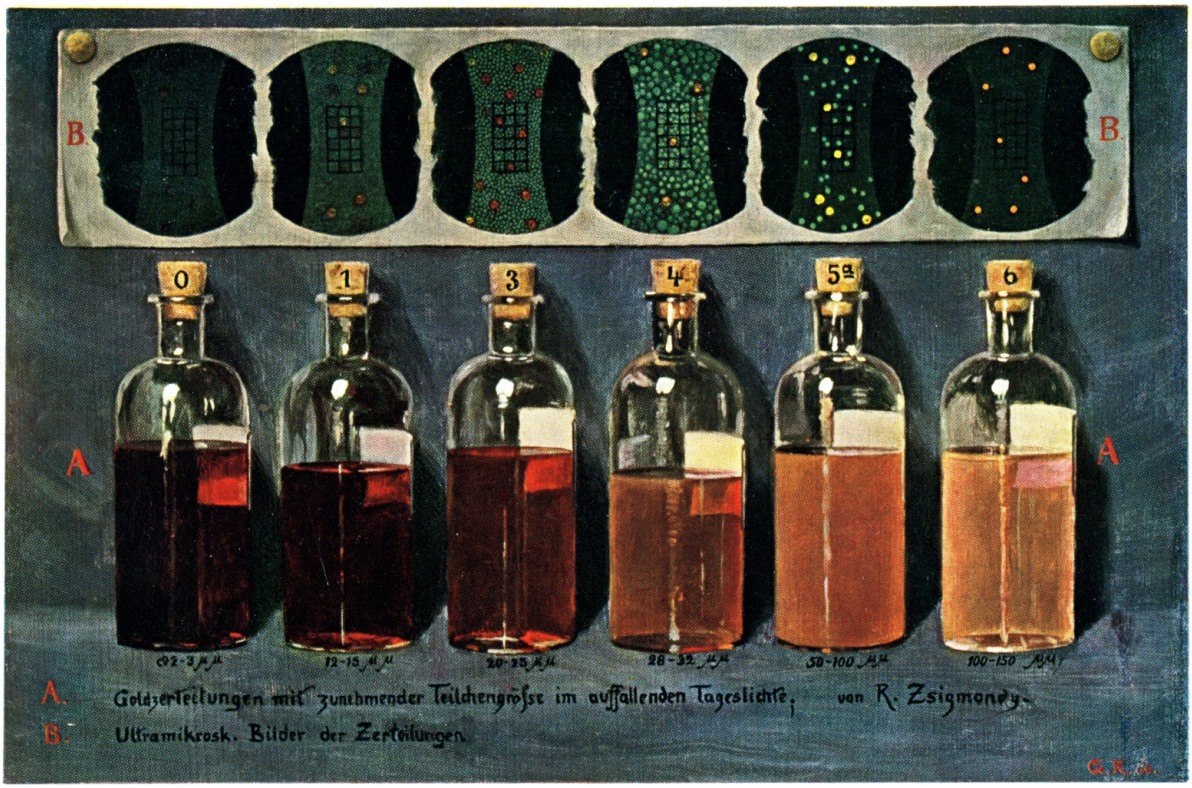
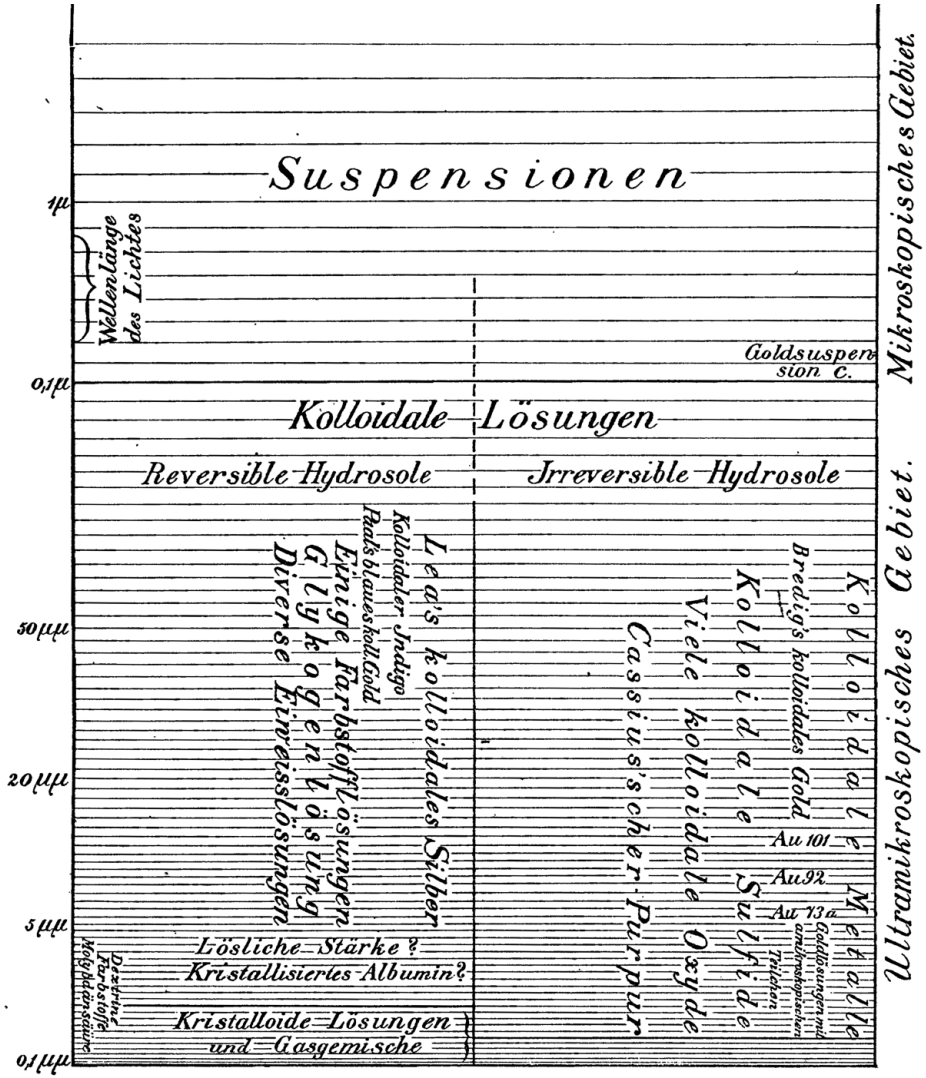


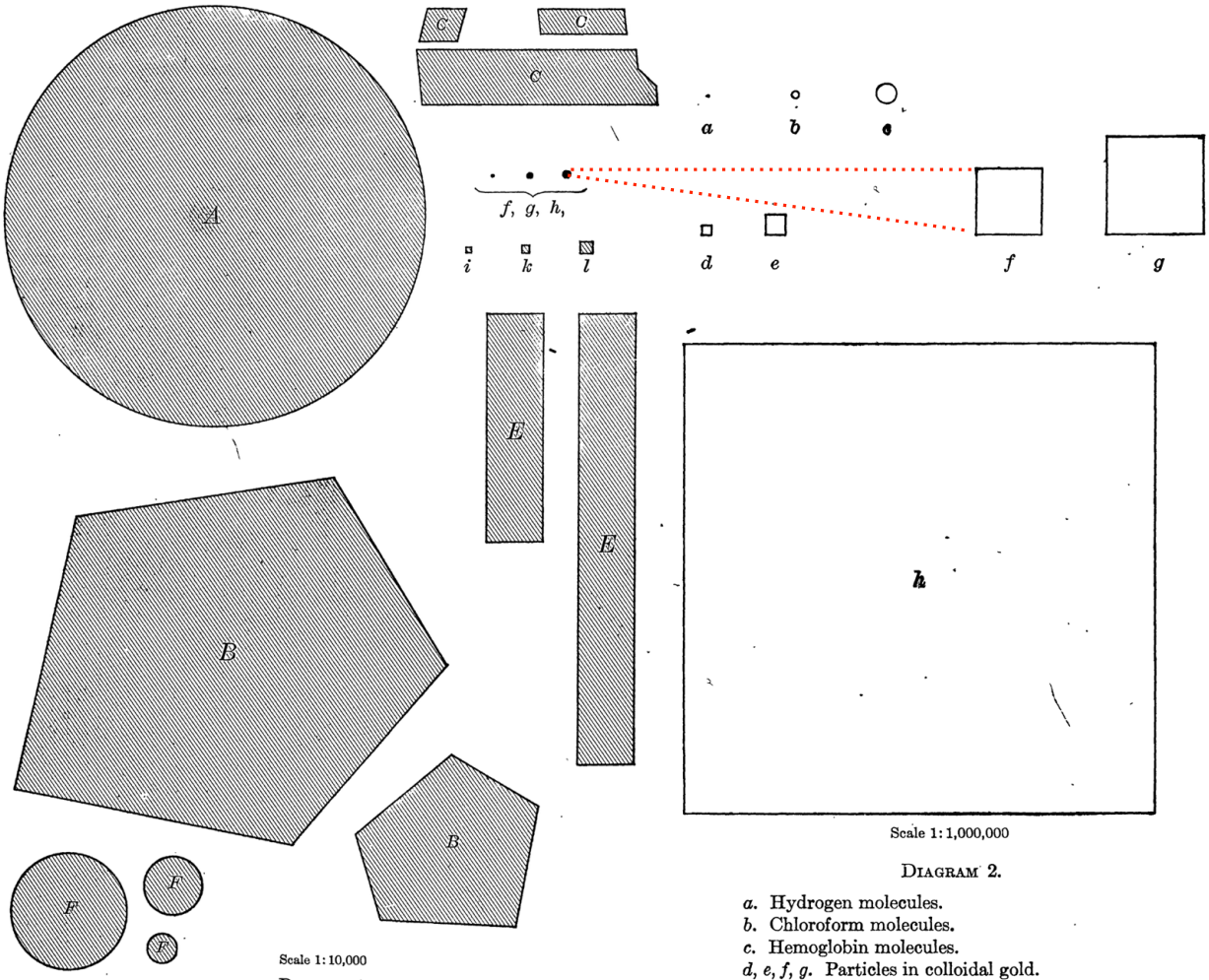
Figure 3.1. Above: schematic layout for Zsigmondy and Siedentopf's slit-ultramicroscope. The elaborate illumination device focuses polarized light a thin slit *S,* resulting in a flat, double-cone shaped field of light entering through the side of a fluid sample held on the microscope stage. Below: Solutions of 0.005% colloidal gold, in order of increasing particle size, and their appearances when viewed through the slit ultramicroscope. In samples 0–4, the gold particles are the green particles, fainter and smaller in 0 and larger and brighter in 4; the red and orange particles in 0–4 are distortions caused by dust. In 5a the large gold particles are both green and yellow, while in 6 the bright orange gold particles are so large they sediment.
Richard Adolf Zsigmondy, *Colloids and the Ultramicroscope: A Manual of Colloid Chemistry and Ultramicroscopy*, trans. Jerome Alexander (New York: J. Wiley & Sons, 1914).





Einteilung der kolloidalen Lösungen
nach der Größe der in ihnen enthaltenen Teilchen und nach ihrem Verhalten beim Eintrocknen.

Figure 3.2. Richard Zsigmondy's graphical explanation for the continuity of suspensions, colloidal solutions, and crystalloid/pure/molecular solutions, while showing a division between reversible and irreversible hydrosols. Richard Zsigmondy, *Zur Erkenntnis der Kolloide: Über irreversible Hydrosole und Ultramikroskopie*. (Jena: Gustav Fischer, 1905).



A. Corpuscles in human blood.
B. Fragments of rice starch.
C. Particles in kaolin suspensions.
E. Bacilli from a diseased spleen.

DIAGRAM 1.

F. Globular bacilli.
f, g, h. Particles in colloidal gold.
i, k, l. Particles that precipitate from gold suspensions.

(17)

DIAGRAM 2.

a. Hydrogen molecules.
b. Chloroform molecules.
c. Hemoglobin molecules.
d, e, f, g. Particles in colloidal gold.
h. Particles that precipitate from gold suspensions.

Figure 3.3. Richard Zsigmondy's diagrams of relative colloidal particle size; *j, k,* and *l* in the left, diagram roughly correspond to *d, e, f,* and *g* in the right, as indicated by the dotted red line. From Richard Zsigmondy, "Kolloidchemie," in *The Chemistry of Colloids*, trans. Ellwood Barker Spear (New York: John Wiley & Sons, 1917), 17–18.

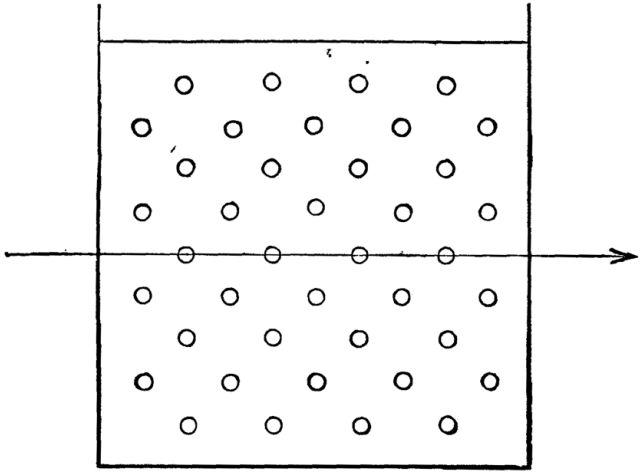


FIG. 3. — Diagram illustrating the concept, dispersed system.

Figure 3.4. Above: Wolfgang Ostwald's schematic of a dispersed system. Below: Relationship between internal surface in a disperse system and particle size.

TABLE 1.—INCREASE IN THE SURFACE OF A CUBE WITH PROGRESSIVE DECIMAL SUBDIVISION

Length of one edge			Number of cubes	Total surface	Specific surface
1	cm.		1	6 square cm.	6
1	mm.	$= 1 \times 10^{-1}$ cm.	10^{3}	60 square cm.	6.10^{1}
0.1	mm.	$= 1 \times 10^{-2}$ cm.	10^{6}	600 square cm.	6.10^{2}
0.01	mm.	$= 1 \times 10^{-3}$ cm.	10^{9}	6000 square cm.	6.10^{3}
1.0	μ	$= 1 \times 10^{-4}$ cm.	10^{12}	6 square m.	6.10^{4}
0.1	μ	$= 1 \times 10^{-5}$ cm.	10^{15}	60 square m.	6.10^{5}
0.01	μ	$= 1 \times 10^{-6}$ cm.	10^{18}	600 square m.	6.10^{6}
1.0	$\mu\mu$	$= 1 \times 10^{-7}$ cm.	10^{21}	6000 square cm.	6.10^{7}
0.1	$\mu\mu$	$= 1 \times 10^{-8}$ cm.	10^{24}	6 hectares	6.10^{8}
0.01	$\mu\mu$	$= 1 \times 10^{-9}$ cm.	10^{27}	60 hectares	6.10^{9}
0.001	$\mu\mu$	$= 1 \times 10^{-10}$ cm.	10^{30}	6 square km.	6.10^{10}

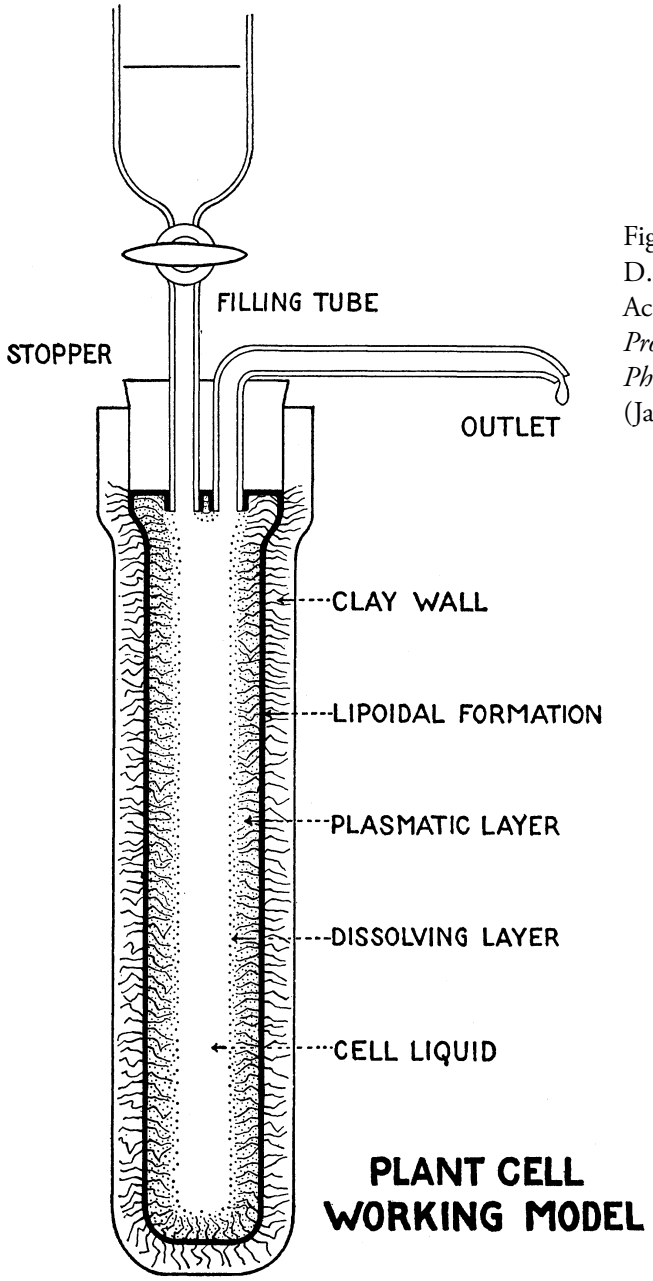


Figure 3.5. MacDougal's artificial cell. D. T. MacDougal, "The Probable Action of Lipoids in Growth," *Proceedings of the American Philosophical Society* 61, no. 1 (January 1922): 33–52.

FIG. 1. Artificial cell designed to illustrate variations in outer wall and plasmatic layer. The clay wall is that of a filter thimble such as is used in the Livingston evaporimeter. The lipoidal layer is drawn heavily out of proportion to illustrate more clearly the processes extending into the wall and the plasmatic layer. The plasmatic layer in the experiments described in this paper was composed of agar, agar-gelatine, or modified mixtures. The cell was submerged to the top of the stopper in operation.

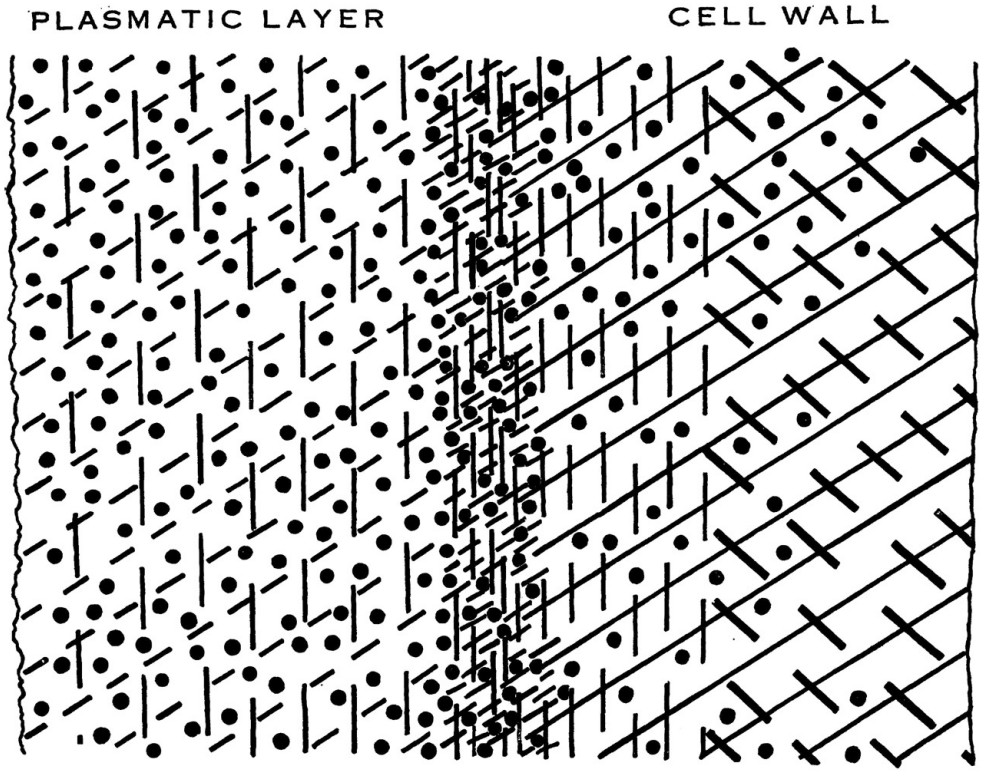


FIG. 1. Diagram of the arrangement of material in the plasmatic layer and cell-wall. / Cellulose. \ Pectin. | Mucilages. / Proteins. ● Fatty substances.

Figure 3.6. D. T. MacDougal's schematic of the colloidal arrangement of the cell wall, lipoidal membrane, and protoplasmic body; this is one of the only schematic, didactic images of the colloidal structure of the protoplasm, and its rarity is perhaps accentuated by the emphasis on instrumental measurement in colloid chemistry. D. T. MacDougal, "The Arrangement and Action of Material in the Plasmatic Layers and Cell-Walls of Plants," *Proceedings of the American Philosophical Society* 63, no. 1 (January 1924): 76–93, on 77.

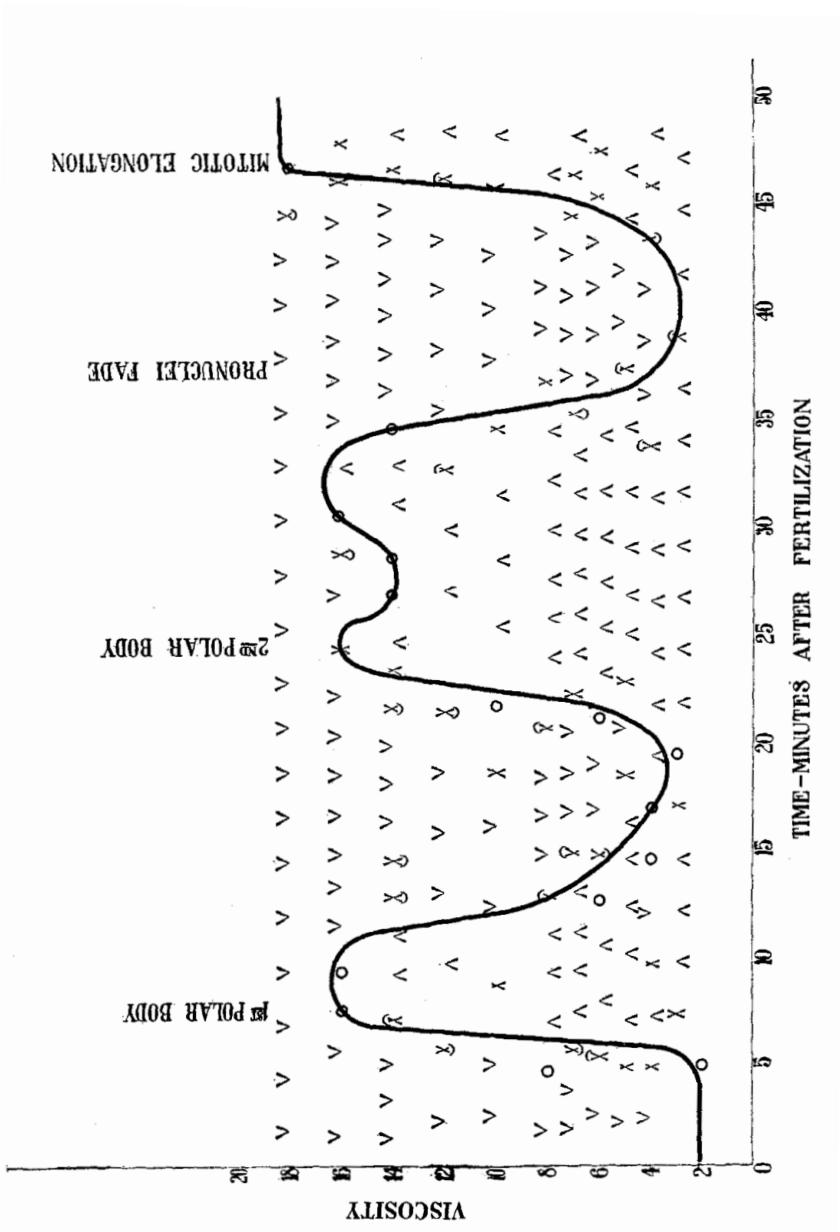


Figure 3.7. One of the results from L. V. Heilbrunn's decades of gently centrifuging marine animal eggs: a plot of fertilization and mitosi events against viscosity. Lewis Victor Heilbrunn, "Protoplasmic Viscosity Changes during Mitosis," *Journal of Experimental Zoology* 34, no. 3 (1921): 416–47.

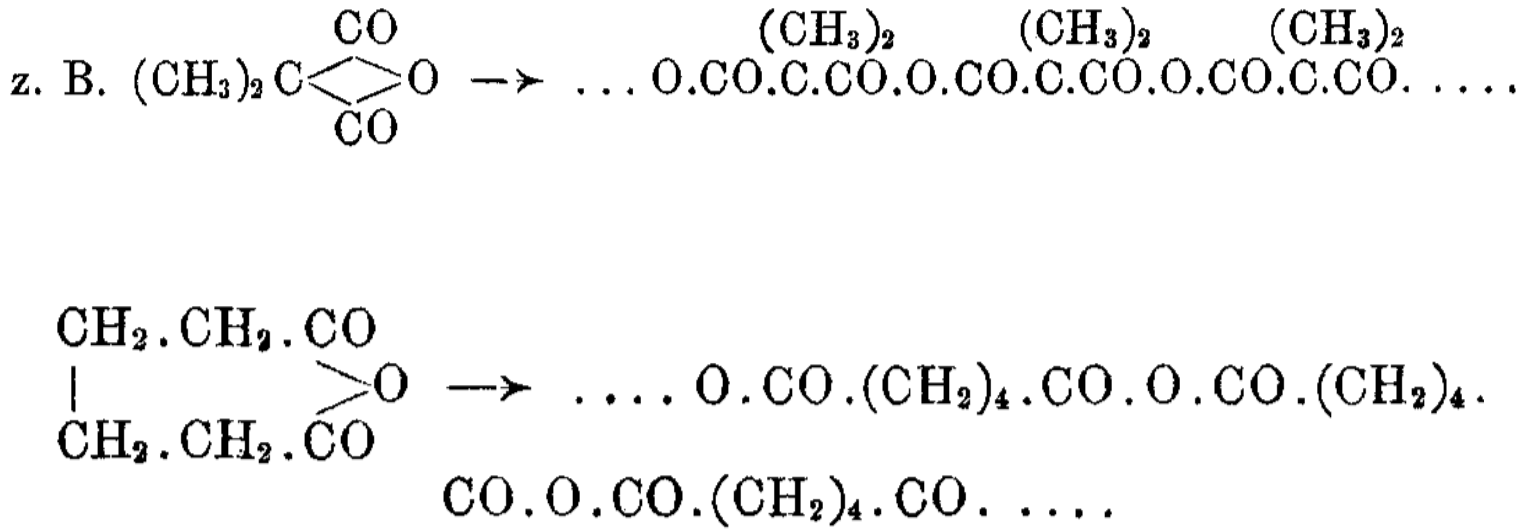


Figure 3.8. Hermann Staudinger's first high-polymer macromolecules. Note the ellipses, indicating his belief that unlimited polymerzation is possible. "Über Polymerisation," *Berichte der deutschen chemischen Gesellschaft* 53, no. 6 (June 12, 1920): 1073–85.

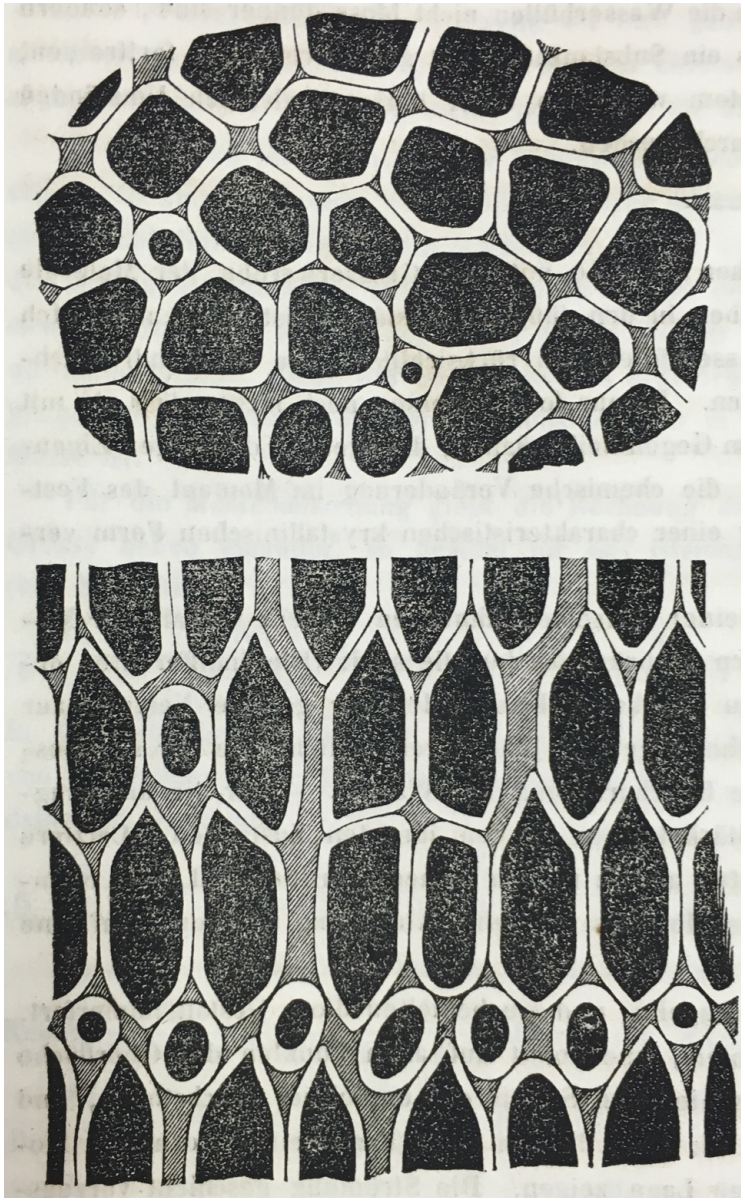
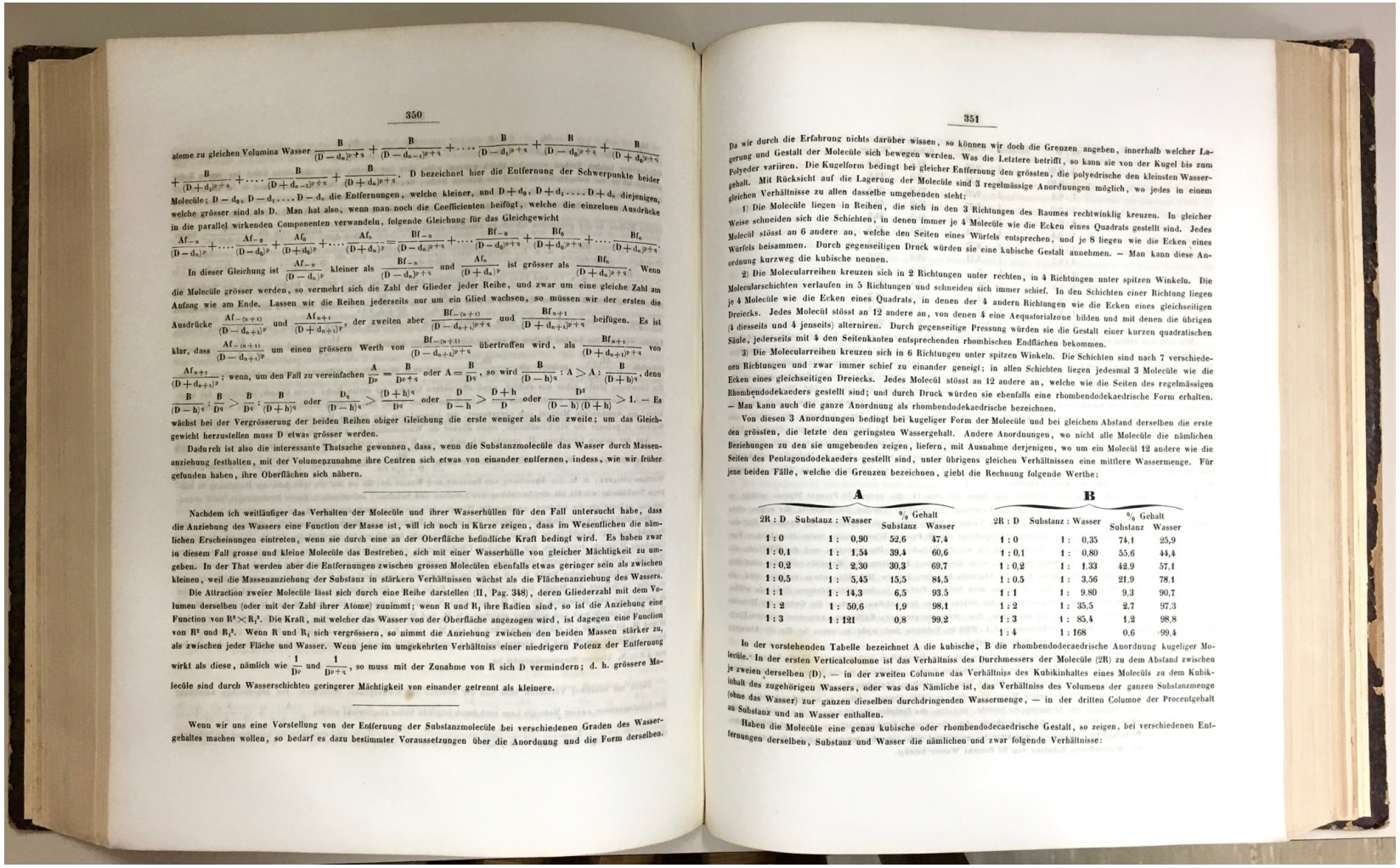


Figure 4.1. Carl Nägeli's 1858 schematic diagrams of "molecular" (later micellar) structure, showing the molecules of starch in black, the "watery atmosphere" in white, and more concentrated areas of fluid in grey. The upper diagram is of the surface of a starch granule, the lower diagram is of part of a radial cross section. Nägeli neither saw nor made such a cross section of starch granules.

Carl Nägeli, *Die Stärkekörner: Morphologische, physiologische, chemisch-physicalische und systematisch-botanische Monographie* (Friedrich Schulthess, 1858), 362.



350

atome zu gleichen Volumina Wasser $\frac{B}{(D-d_n)^{p+q}} + \frac{B}{(D-d_{n-1})^{p+q}} + \cdots \frac{B}{(D-d_1)^{p+q}} + \frac{B}{(D-d_0)^{p+q}} + \frac{B}{(D+d_0)^{p+q}}$

$+ \frac{B}{(D+d_1)^{p+q}} + \cdots \frac{B}{(D+d_{n-1})^{p+q}} + \frac{B}{(D+d_n)^{p+q}}$. D bezeichnet hier die Entfernung der Schwerpunkte beider Molecüle; $D-d_0$, $D-d_1 \ldots D-d_n$ die Entfernungen, welche kleiner, und $D+d_0$, $D+d_1 \ldots D+d_n$ diejenigen, welche grösser sind als D. Man hat also, wenn man noch die Coefficienten beifügt, welche die einzelnen Ausdrücke in die parallel wirkenden Componenten verwandeln, folgende Gleichung für das Gleichgewicht

$$\frac{Af_{-n}}{(D-d_n)^p} + \cdots \frac{Af_{-0}}{(D-d_0)^p} + \frac{Af_0}{(D+d_0)^p} + \cdots \frac{Af_n}{(D+d_n)^p} = \frac{Bf_{-n}}{(D-d_n)^{p+q}} + \cdots \frac{Bf_{-0}}{(D-d_0)^{p+q}} + \frac{Bf_0}{(D+d_0)^{p+q}} + \cdots \frac{Bf_n}{(D+d_n)^{p+q}}.$$

In dieser Gleichung ist $\frac{Af_{-n}}{(D-d_n)^p}$ kleiner als $\frac{Bf_{-n}}{(D-d_n)^{p+q}}$ und $\frac{Af_n}{(D+d_n)^p}$ ist grösser als $\frac{Bf_n}{(D+d_n)^{p+q}}$. Wenn die Molecüle grösser werden, so vermehrt sich die Zahl der Glieder jeder Reihe, und zwar um eine gleiche Zahl am Anfang wie am Ende. Lassen wir die Reihen jederseits nur um ein Glied wachsen, so müssen wir der ersten die Ausdrücke $\frac{Af_{-(n+1)}}{(D-d_{n+1})^p}$ und $\frac{Af_{n+1}}{(D+d_{n+1})^p}$, der zweiten aber $\frac{Bf_{-(n+1)}}{(D-d_{n+1})^{p+q}}$ und $\frac{Bf_{n+1}}{(D+d_{n+1})^{p+q}}$ beifügen. Es ist klar, dass $\frac{Af_{-(n+1)}}{(D-d_{n+1})^p}$ um einen grössern Werth von $\frac{Bf_{-(n+1)}}{(D-d_{n+1})^{p+q}}$ übertroffen wird, als $\frac{Bf_{n+1}}{(D+d_{n+1})^{p+q}}$ von $\frac{Af_{n+1}}{(D+d_{n+1})^p}$; wenn, um den Fall zu vereinfachen $\frac{A}{D^p} = \frac{B}{D^{p+q}}$ oder $A = \frac{B}{D^q}$, so wird $\frac{B}{(D-h)^q} : A > A : \frac{B}{(D+h)^q}$, denn $\frac{B}{(D-h)^q} : \frac{B}{D^q} > \frac{B}{D^q} : \frac{B}{(D+h)^q}$ oder $\frac{D_q}{(D-h)^q} > \frac{(D+h)^q}{D^q}$ oder $\frac{D}{D-h} > \frac{D+h}{D}$ oder $\frac{D^2}{(D-h)(D+h)} > 1$. — Es wächst bei der Vergrösserung der beiden Reihen obiger Gleichung die erste weniger als die zweite; um das Gleichgewicht herzustellen muss D etwas grösser werden.

Dadurch ist also die interessante Thatsache gewonnen, dass, wenn die Substanzmolecüle das Wasser durch Massenanziehung festhalten, mit der Volumenzunahme ihre Centren sich etwas von einander entfernen, indess, wie wir früher gefunden haben, ihre Oberflächen sich nähern.

Nachdem ich weitläufiger das Verhalten der Molecüle und ihrer Wasserhüllen für den Fall untersucht habe, dass die Anziehung des Wassers eine Function der Masse ist, will ich noch in Kürze zeigen, dass im Wesentlichen die nämlichen Erscheinungen eintreten, wenn sie durch eine an der Oberfläche befindliche Kraft bedingt wird. Es haben zwar in diesem Fall grosse und kleine Molecüle das Bestreben, sich mit einer Wasserhülle von gleicher Mächtigkeit zu umgeben. In der That werden aber die Entfernungen zwischen grossen Molecülen ebenfalls etwas geringer sein als zwischen kleinen, weil die Massenanziehung der Substanz in stärkern Verhältnissen wächst als die Flächenanziehung des Wassers.

Die Attraction zweier Molecüle lässt sich durch eine Reihe darstellen (II, Pag. 348), deren Gliederzahl mit dem Volumen derselben (oder mit der Zahl ihrer Atome) zunimmt; wenn R und R_1 ihre Radien sind, so ist die Anziehung eine Function von $R^3 \times R_1^3$. Die Kraft, mit welcher das Wasser von der Oberfläche angezogen wird, ist dagegen eine Function von R^2 und R_1^2. Wenn R und R_1 sich vergrössern, so nimmt die Anziehung zwischen den beiden Massen stärker zu, als zwischen jeder Fläche und Wasser. Wenn jene im umgekehrten Verhältniss einer niedrigern Potenz der Entfernung wirkt als diese, nämlich wie $\frac{1}{D^p}$ und $\frac{1}{D^{p+q}}$, so muss mit der Zunahme von R sich D vermindern; d. h. grössere Molecüle sind durch Wasserschichten geringerer Mächtigkeit von einander getrennt als kleinere.

Wenn wir uns eine Vorstellung von der Entfernung der Substanzmolecüle bei verschiedenen Graden des Wassergehaltes machen wollen, so bedarf es dazu bestimmter Voraussetzungen über die Anordnung und die Form derselben.

351

Da wir durch die Erfahrung nichts darüber wissen, so können wir doch die Grenzen angeben, innerhalb welcher Lagerung und Gestalt der Molecüle sich bewegen werden. Was die Letztere betrifft, so kann sie von der Kugel bis zum Polyeder variiren. Die Kugelform bedingt bei gleicher Entfernung den grössten, die polyedrische den kleinsten Wassergehalt. Mit Rücksicht auf die Lagerung der Molecüle sind 3 regelmässige Anordnungen möglich, wo jedes in einem gleichen Verhältnisse zu allen dasselbe umgebenden steht:

1) Die Molecüle liegen in Reihen, die sich in den 3 Richtungen des Raumes rechtwinklig kreuzen. In gleicher Weise schneiden sich die Schichten, in denen immer je 4 Molecüle wie die Ecken eines Quadrats gestellt sind. Jedes Molecül stässt an 6 andere an, welche den Seiten eines Würfels entsprechen, und je 8 liegen wie die Ecken eines Würfels beisammen. Durch gegenseitigen Druck würden sie eine kubische Gestalt annehmen. — Man kann diese Anordnung kurzweg die kubische nennen.

2) Die Molecularreihen kreuzen sich in 2 Richtungen unter rechten, in 4 Richtungen unter spitzen Winkeln. Die Molecularschichten verlaufen in 5 Richtungen und schneiden sich immer schief. In den Schichten einer Richtung liegen je 4 Molecüle wie die Ecken eines Quadrats, in denen der 4 andern Richtungen wie die Ecken eines gleichseitigen Dreiecks. Jedes Molecül stösst an 12 andere an, von denen 4 eine Aequatorialzone bilden und mit denen die übrigen (4 diesseits und 4 jenseits) alterniren. Durch gegenseitige Pressung würden sie die Gestalt einer kurzen quadratischen Säule, jederseits mit 4 den Seitenkanten entsprechenden rhombischen Endflächen bekommen.

3) Die Molecularreihen kreuzen sich in 6 Richtungen unter spitzen Winkeln. Die Schichten sind nach 7 verschiedenen Richtungen und zwar immer schief zu einander geneigt; in allen Schichten liegen jedesmal 3 Molecüle wie die Ecken eines gleichseitigen Dreiecks. Jedes Molecül stösst an 12 andere an, welche wie die Seiten des regelmässigen Rhombendodekaeders gestellt sind; und durch Druck würden sie ebenfalls eine rhombendodekaedrische Form erhalten. — Man kann auch die ganze Anordnung als rhombendodekaedrische bezeichnen.

Von diesen 3 Anordnungen bedingt bei kugeliger Form der Molecüle und bei gleichem Abstand derselben die erste den grössten, die letzte den geringsten Wassergehalt. Andere Anordnungen, wo nicht alle Molecüle die nämlichen Beziehungen zu den sie umgebenden zeigen, liefern, mit Ausnahme derjenigen, wo um ein Molecül 12 andere wie die Seiten des Pentagondodekaeders gestellt sind, unter übrigens gleichen Verhältnissen eine mittlere Wassermenge. Für jene beiden Fälle, welche die Grenzen bezeichnen, giebt die Rechnung folgende Werthe:

A				B			
2R : D	Substanz : Wasser	% Gehalt Substanz	% Gehalt Wasser	2R : D	Substanz : Wasser	% Gehalt Substanz	% Gehalt Wasser
1 : 0	1 : 0,90	52,6	47,4	1 : 0	1 : 0,35	74,1	25,9
1 : 0,1	1 : 1,54	39,4	60,6	1 : 0,1	1 : 0,80	55,6	44,4
1 : 0,2	1 : 2,30	30,3	69,7	1 : 0,2	1 : 1,33	42,9	57,1
1 : 0,5	1 : 5,45	15,5	84,5	1 : 0,5	1 : 3,56	21,9	78,1
1 : 1	1 : 14,3	6,5	93,5	1 : 1	1 : 9,80	9,3	90,7
1 : 2	1 : 50,6	1,9	98,1	1 : 2	1 : 35,5	2,7	97,3
1 : 3	1 : 121	0,8	99,2	1 : 3	1 : 85,4	1,2	98,8
				1 : 4	1 : 168	0,6	99,4

In der vorstehenden Tabelle bezeichnet A die kubische, B die rhombendodecaedrische Anordnung kugeliger Molecüle. In der ersten Verticalcolumne ist das Verhältniss des Durchmessers der Molecüle (2R) zu dem Abstand zwischen je zweien derselben (D), — in der zweiten Columne das Verhältniss des Kubikinhaltes eines Molecüls zu dem Kubikinhalt des zugehörigen Wassers, oder was das Nämliche ist, das Verhältniss des Volumens der ganzen Substanzmenge (ohne das Wasser) zur ganzen dieselben durchdringenden Wassermenge, — in der dritten Columne der Procentgehalt an Substanz und an Wasser enthalten.

Haben die Molecüle eine genau kubische oder rhombendodecaedrische Gestalt, so zeigen, bei verschiedenen Entfernungen derselben, Substanz und Wasser die nämlichen und zwar folgende Verhältnisse:

Figure 4.2. Two pages from chapter 10 of Nägeli's *Die Stärkekörner*, "Hypothesis of molecular constitution." On the left: typical mathematical equations for calculating Nägeli's hypothetical intermolecular force. On the lower right, tables of hypothetical diameters of starch molecules/micelles as they relate to the proportion of water to starch in the starch granule; cubic molecules under "A", dodecahedral molecules under "B". Carl Nägeli, *Die Stärkekörner: Morphologische, physiologische, chemisch-physicalische und systematisch-botanische Monographie* (Friedrich Schulthess, 1858), 350–51.

Proteinkrystalloide lassen einen Theil
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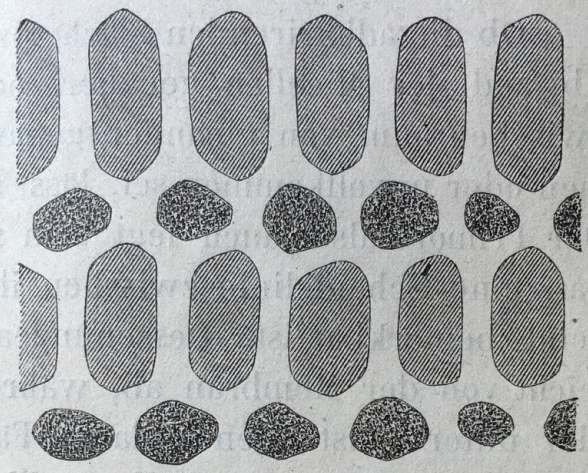

Figur 219.

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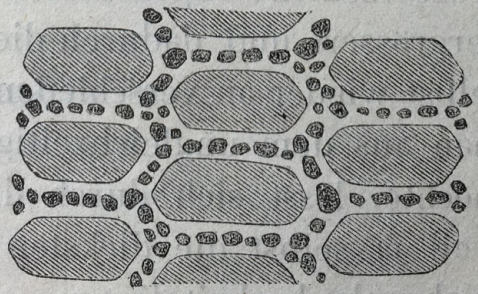


Figur 220.

g, dass die Molecüle verschiedener

Figure 4.3. Figures of mixed-molecular/micellar crystalloids, according to Nägeli, suggesting how one birefringent substance (oblong, grey micelles) can be intermixed with another, optically isotropic substance in two different ways. Carl Nägeli and Simon Schwendener, *Das Mikroskop: Theorie und Anwendung Desselben*, 2nd ed. (Leipzig: W. Engelmann, 1877), 425. (These were originally Figures 200 and 201 in the first, 1867 edition of *Das Mikroskop*.)

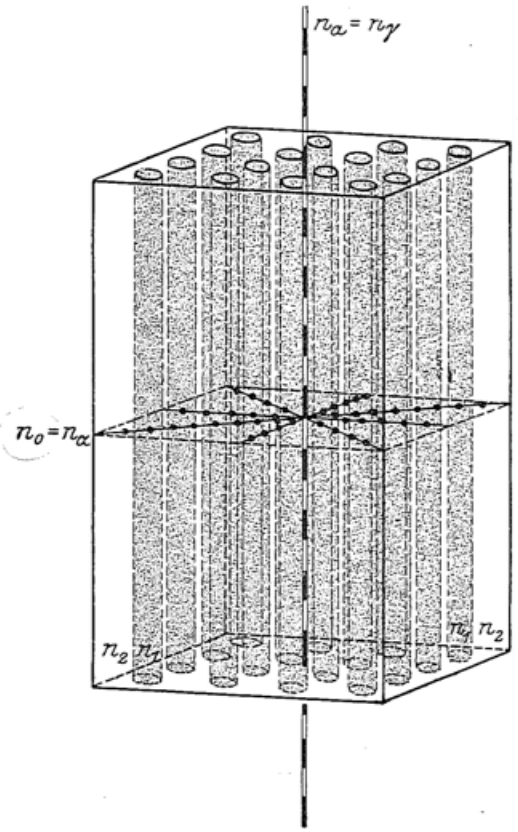


Fig. 25. Zylindermischkörper. $n_a > n_o$, optisch positiv.
$= n_\gamma$, $= n_\alpha$.

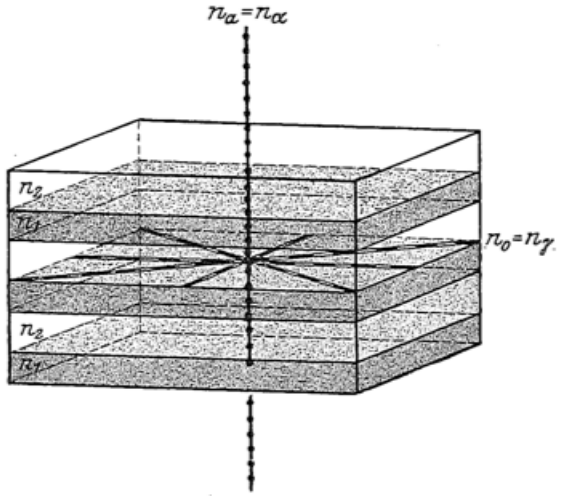


Fig. 26.
Schichtenmischkörper. $n_a < n_o$, optisch negativ.

Figure 4.4. Wiener mixed bodies: rodlet mixed body on the left, platelet mixed body on right. Hermann Ambronn and Albert Frey, *Das Polarisationsmikroskop: Seine Anwendung in der Kolloidforschung und in der Färberei*, Kolliodforschung in Einzeldarstellungen, Bd. 5 (Leipzig: Akademische Verlagsgesellschaft, 1926), 114, 119.

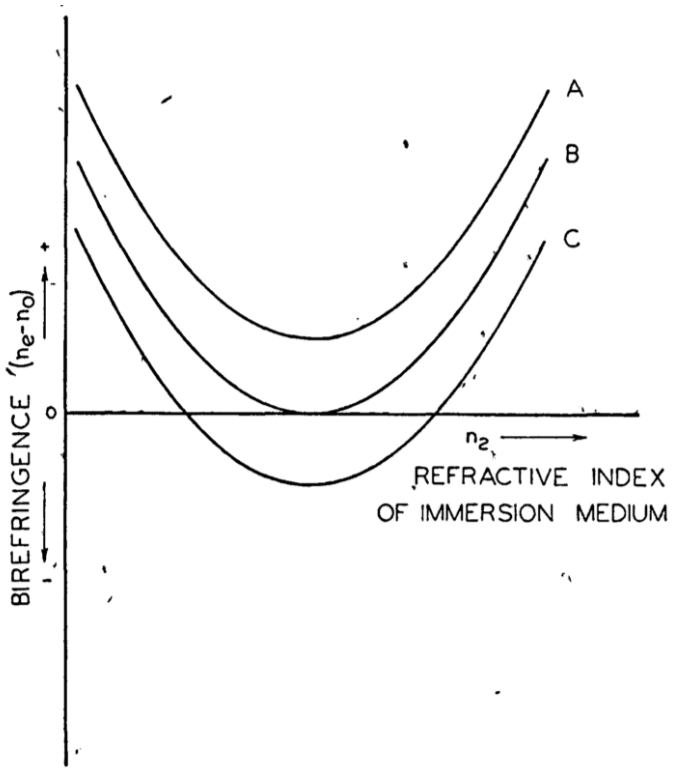


FIG. 1.—Method of determining sign and relative amount of form and crystalline birefringence by immersion technic. *A* indicates positive form and positive crystalline birefringence. *B* indicates positive form and no crystalline birefringence. *C* indicates positive form and negative crystalline birefringence.

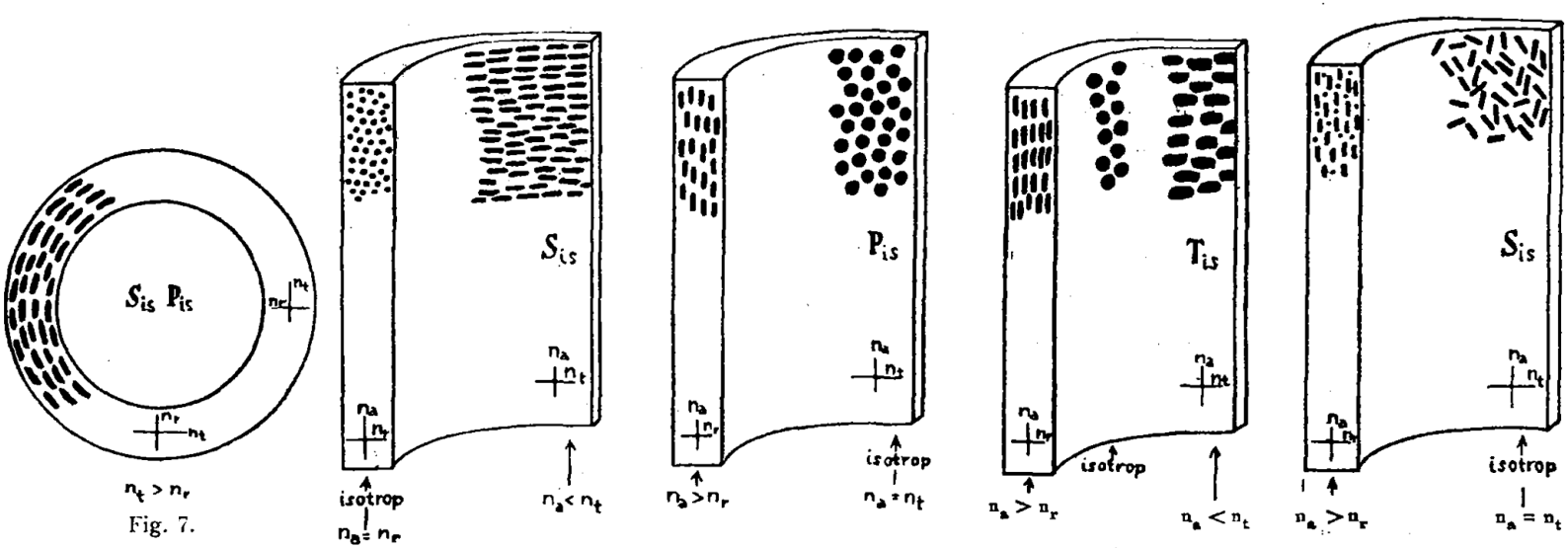
Figure 4.5. Example of different birefringence curves for three cases of rodlet form birefringence in a Wiener mixed-body, as the refractive index of the immersion medium (n_2) increases. The curves for platelet form birefringence would be similar, but simply mirrored across the x axis. This graph from Francis O. Schmitt, "Tissue Ultrastructure Analysis: Polarized Light Method," in *Medical Physics*, ed. Otto Glasser, vol. 1, 3 vols. (Chicago: The Year Book Publishers, inc., 1944), 1586–91.

TABLE I

MORPHOLOGY

Morphological hierarchy		Instruments of research	Scales	Order of magnitude
Organs	Organography	Eye, magnif. glass	mm scale	$>$ 0.1 mm
Tissues	Histology	Microscope	Micrometer	$>$ 1 μ
Cells	Cytology	Immersion and ultraviolet microscope	Wave-lengths of light	$>$ 0.1 μ
Fine-structure	Micellar studies	Polarisation microscope	Fraction of wave-length	$<$ 0.1 μ
Molecule structure	Structural chemistry	X-rays	Wave-length of X-rays	$>$ 1 Å
Atom structure	Electron theory	Electron rays	Wave-length of electron-rays	$<$ 0.1 Å

Figure 4.6. Frey-Wyssling's table of morphological hierarchies (translated from the 1938 version). Albert Frey-Wyssling, *Submicroscopic Morphology of Protoplasm and Its Derivatives*, trans. J.J. Hermans and Mary Hollander (New York: Elsevier, 1948), 4.



Formdoppelbrechung bei zirkularer Anordnung der Mizelle.

Figure 4.7. Albert Frey's micellar diagrams of form and intrinsic birefringence of circularly-arranged micelles, achieved by stirring a colloid in a cylinder, and examining it with hand held field polarizers. Albert Frey, "Doppelbrechung der Dispersoide," *Kolloidchemische Beihefte* 20, no. 6 (January 1925): 209–43.

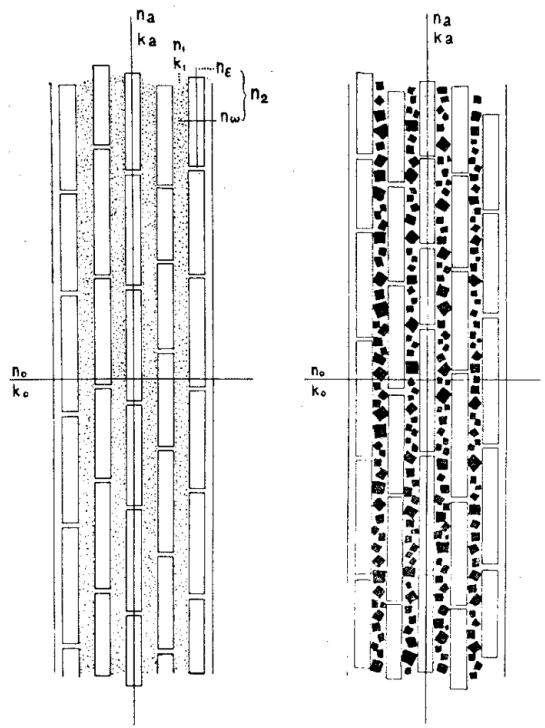


Fig. 10. Micellarstruktur der Bastfaserwandung

a) Jodfärbung; Jod molekular (?) eingelagert

b) Silberfärbung; Silber als ultramikroskopische Kriställchen regellos eingelagert

n_a = Brechungsindex ∥ Faserachse

n_o = „ ⊥ „

k_a = Absorptionskoeffizient ∥ Faserasche

k_o = „ ⊥ „

n_1 = Brechungsindex } der Intermicellarsubstanz

k_1 = Absorptionskoeffizient }

n_ε, n_ω = Brechungsindices der Zellulosemicelle

$n_\varepsilon - n_\omega$ = Eigendoppelbrechung = 0,061

Figure 4.8. Albert Frey's conception of dichroic staining of bast fiber with iodine (*a*) and silver chloride (*b*). The white rectangles are the cellulose micelles. Albert Frey, "Das Reich des Ultramikroskopischen in der Biologie," *Protoplasma* 4, no. 1 (May 1928): 139–54.

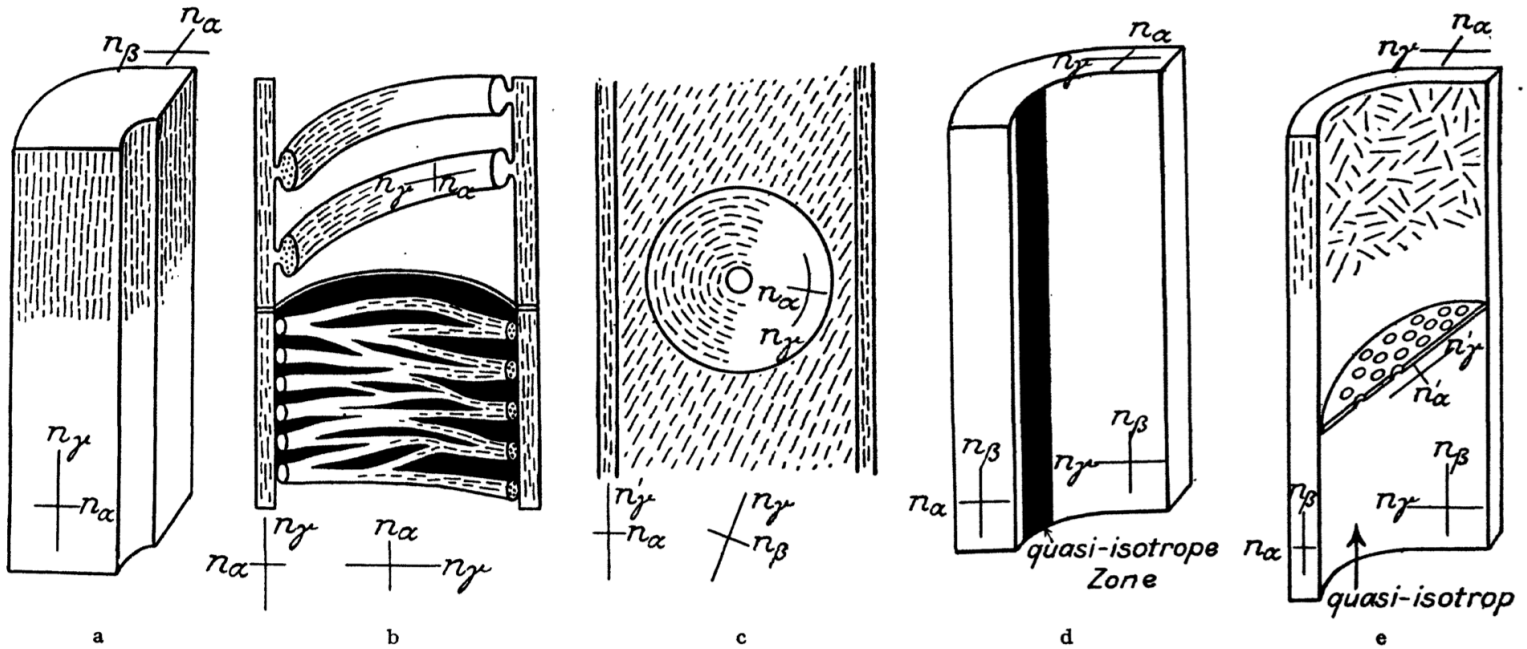


Fig. 8. Optik und wahrscheinliche Micellarstruktur verschiedener Zelltypen[12]: a) Phloemfaser (Ramie) $n_\beta \cong n_\alpha$; b) Spiral- und Netzgefäß; c) Coniferen-Tracheide; d) Milchröhre von Euphorbia; e) Siebröhre von Cucurbita.

Figure 4.9. Albert Frey's micellar diagrams of various plant cell wall types, indicating both the arrangement and orientation of the micelles, as well as the optical properties of each system expressed by refractive indices (*n*). Below: Albert Frey, "Der Submikroskopische Feinbau Der Zellmembranen," *Naturwissenschaften* 15, no. 37 (September 16, 1927): 760–65

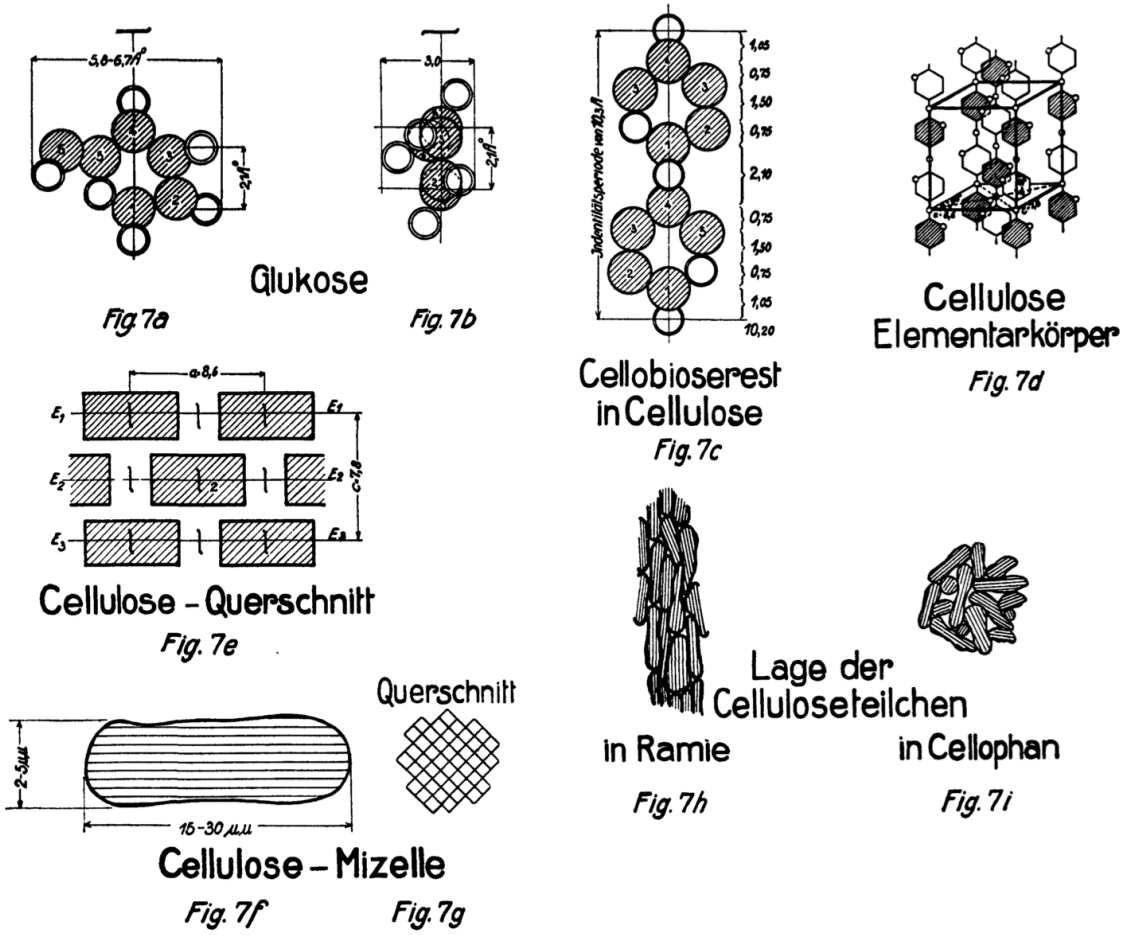


Figure 4.10. Kurt Meyer's schematic diagrams for molecular and micellar structure. (*a*) and (*b*) show glucose in portrait and profile, noting the space between atoms and the size of the whole molecule; (*c*) shows the smallest unit of cellulose, (*d*) the arrangement of cellulose chains into a micelle; (*e*) the spacing between micelles, (*f*) the dimensions of a single cellulose micelle and suggestion of the location of the chain molecules in (*g*); and the orientation of micelles in a ramie fiber (*h*) and more jumbled in cellophane (*i*). Kurt H. Meyer, "Neue Wege in der organischen Strukturlehre und in der Erforschung hochpolymerer Verbindungen," *Naturwissenschaften* 16 (1928): 781–92.

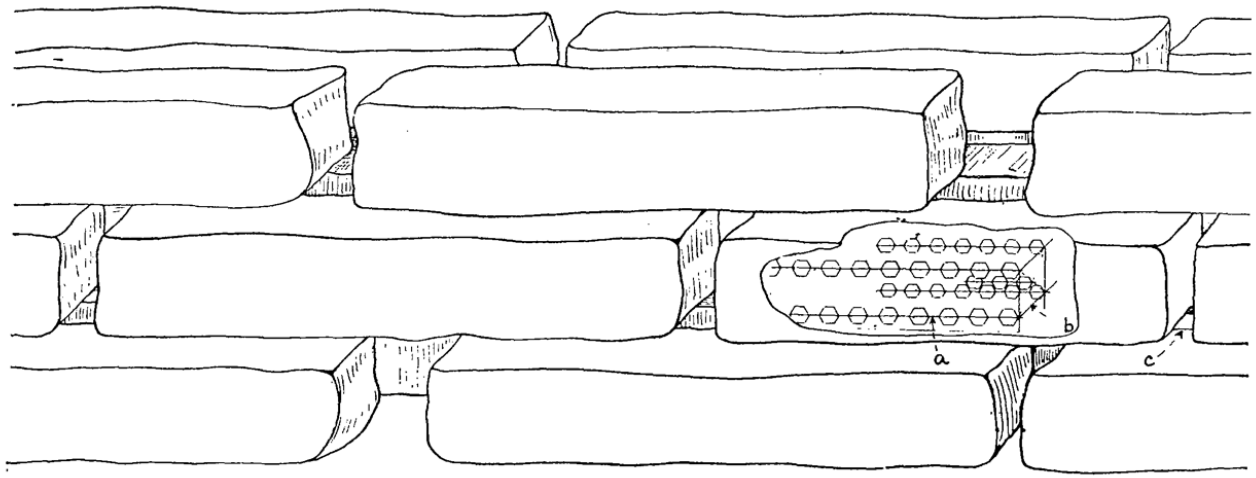


FIG. 6. A number of cellulose micellae, the interior of one of which is, in part, exposed and enlarged to show the chains of glucose residue units: *a* = primary valency forces, *b* = secondary association forces, *c* = tertiary micellar forces.

Figure 4.11. William Seifriz's 1929 brick-like diagram of cellulose micellae, suggesting how individual chains of cellulose are packed in a micellar structure. Frey-Wyssling would later call this an old-fashioned, unmodified Nägelian micellar model. Originally published in William Seifriz, "The Contractility of Protoplasm," *The American Naturalist* 63, no. 688 (September 1929): 410–34; Meyer republished it in Germany for the first time without attribution, Kurt H. Meyer, "Räumliche Vorstellungen über den Bau der Kohlenstoffverbindungen und ihre Verwendung in der Chemie der Hochpolymeren," *Kolloid-Zeitschrift* 53, no. 1 (1930): 8–20.

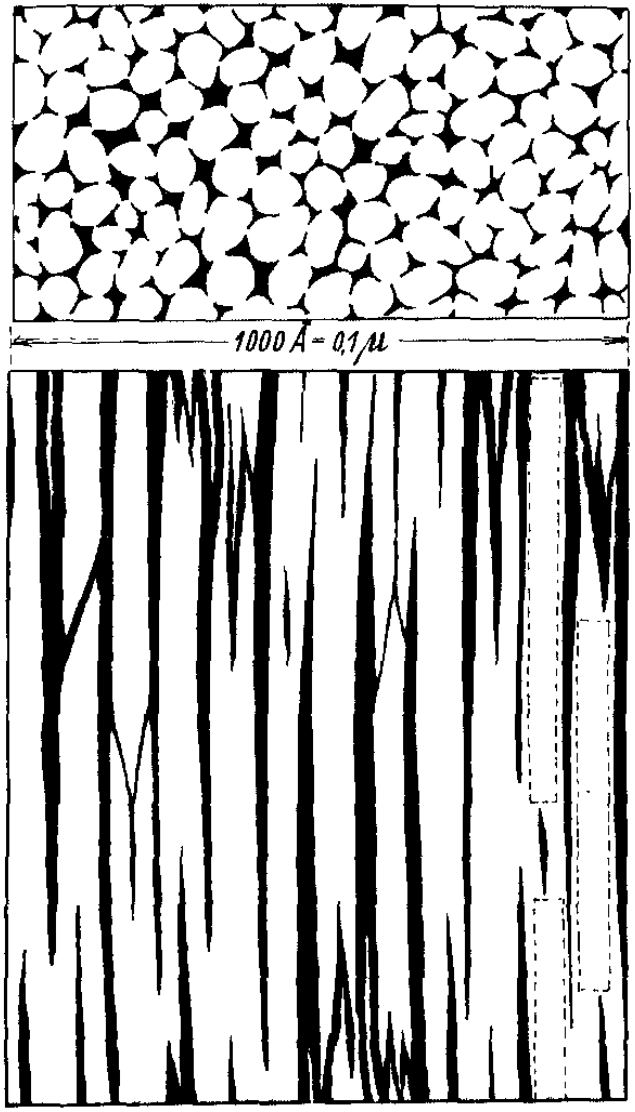


Figure 4.12. Frey-Wyssling's post-1935 micellar "reticular system" model of the plant cell wall. The cellulose in the reticular system is illustrated in white, the intermicellar gaps are in black. The micelles are indicated by the dotted lines in the lower, transverse section diagram. Albert Frey-Wyssling, "Der Aufbau der pflanzlichen Zellwände," *Protoplasma* 25, no. 1 (December 1936): 261–300.

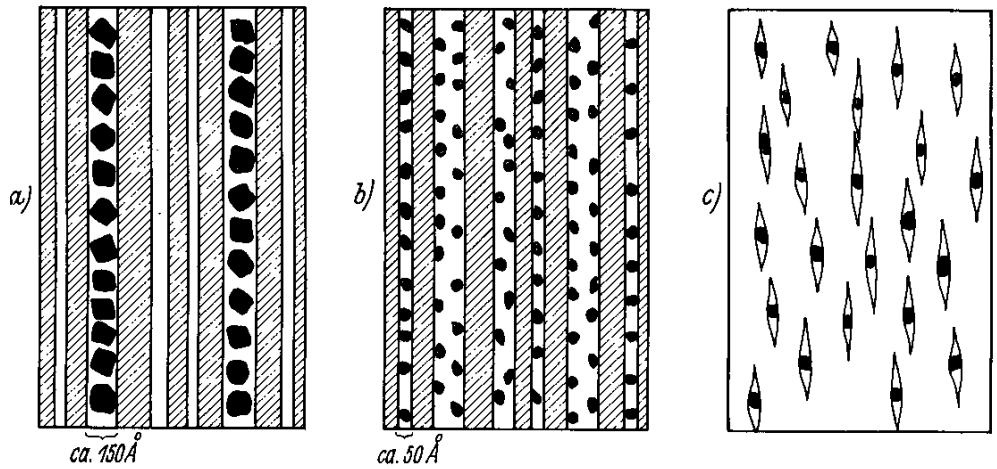


Fig. 10. Beziehung zwischen Goldeinlagerung und Dichroismus. *a*) Große Goldkristallite ($>$ 100 Å) reihenweise in den weiteren Kapillaren: starker Stäbchendichroismus. *b*) Kleinere Kristallite ($\sim$ 50 Å), die sich nicht nur in den weiteren, sondern auch in engeren Räumen befinden. Die Verteilung der Teilchen wird dadurch statistisch gleichmäßiger: schwacher oder fehlender Stäbchendichroismus. *c*) Aufsprengung der Intermicellarräume durch Kristallkeime muß ebenfalls eine $\pm$ gleichmäßige Verteilung der Teilchen zur Folge haben.

Figure 4.13. Highlighting the intermicellar spaces by gold staining, especially in (*c*); micelles are suggested by the grey bars in (*a*) and (*b*). Note the estimated size measurement of the intermicellar space, using the size the gold particles in the dichroic stain. Albert Frey-Wyssling, "Röntgenometrische Vermessung der submikroskopischen Räume in Gerüstsubstanzen," *Protoplasma* 27, no. 1 (December 1937): 372–411.

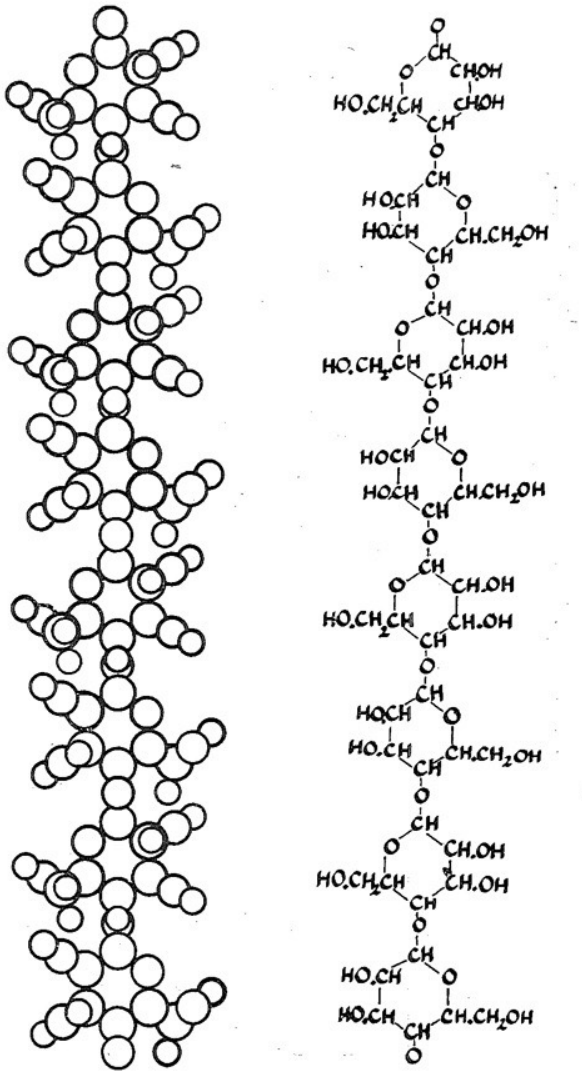


Fig. 47. The atomic arrangement and conventional formula of part of the cellulose chain.

Figure 4.14. Atomic diagram of part of a cellulose chain molecule. From W. T. Astbury, *Fundamentals of Fibre Structure* (London: Oxford University Press, 1933), 110.

TABLE I

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Morphological hierarchy		Instrument of research	Scale	Order of magnitude
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Cells	Cytology	Immersion and ultraviolet microscope	Wavelengths of light	> 0.1 μ
Fine-structure	Micellar studies	Electron microscope	Colloid dimensions	> 1 mμ
Molecule structure	Structural chemistry	X-rays	Wavelength of X-rays	> 1 Å
Atom structure	Electron theory	Electron rays	Wavelength of electron rays	< 0.1 Å

Figure 4.15. Frey-Wyssling's conception of the "The Realm of Morphology" updated in 1953. Note the changes in the fourth row, compared to Figure 4.7. Albert Frey-Wyssling, *Submicroscopic Morphology of Protoplasm*, trans. Mary Hollander, 2nd English ed. (Amsterdam: Elsevier, 1953), 6.

FIGURE 8.
FIBRILLAR TEXTURE OF THE SECONDARY WALL OF COTTON HAIRS. (ELECTRON MICROGRAPH BY K. MÜHLETHALER; LAB. OF DR. WYCKOFF.)

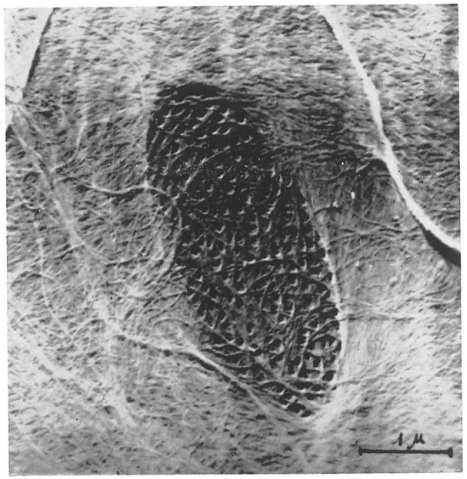


FIGURE 9.
SIMPLE PIT FROM A CELL IN THE GERMINATING ROOT OF CORN. (ELECTRON MICROGRAPH BY K. MÜHLETHALER; LAB. OF DR. WYCKOFF.)

Figure 4.16. Early electron micrographs of cotton fibers, implying direct, visual access to fine structure. No magnification is given. Albert Frey-Wyssling, "The Growth in Surface of the Plant Cell Wall," *Growth* 12, supp. (1948): 151–70.

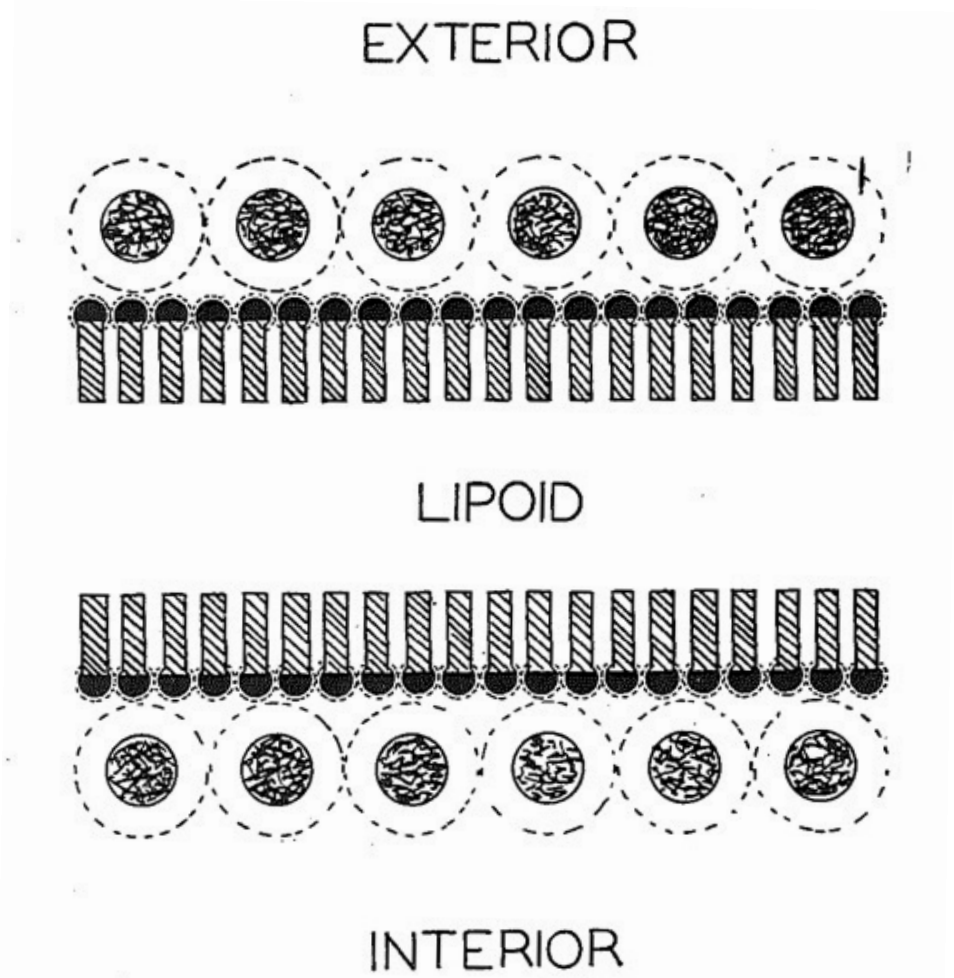


Fig. 1 Schema of molecular conditions at the cell surface.

Figure 5.1. Danielli-Davson model of the cell membrane, a lipid bilayer with spherical protein molecules adsorbed to both surfaces. W. J. Schmidt never worked specifically on cell membrane structure, nor did he ever cite the Danielli-Davson model before 1941. James Frederic Danielli and Hugh Davson, "A Contribution to the Theory of Permeability of Thin Films," *Journal of Cellular and Comparative Physiology* 5, no. 4 (February 1935): 495–508.

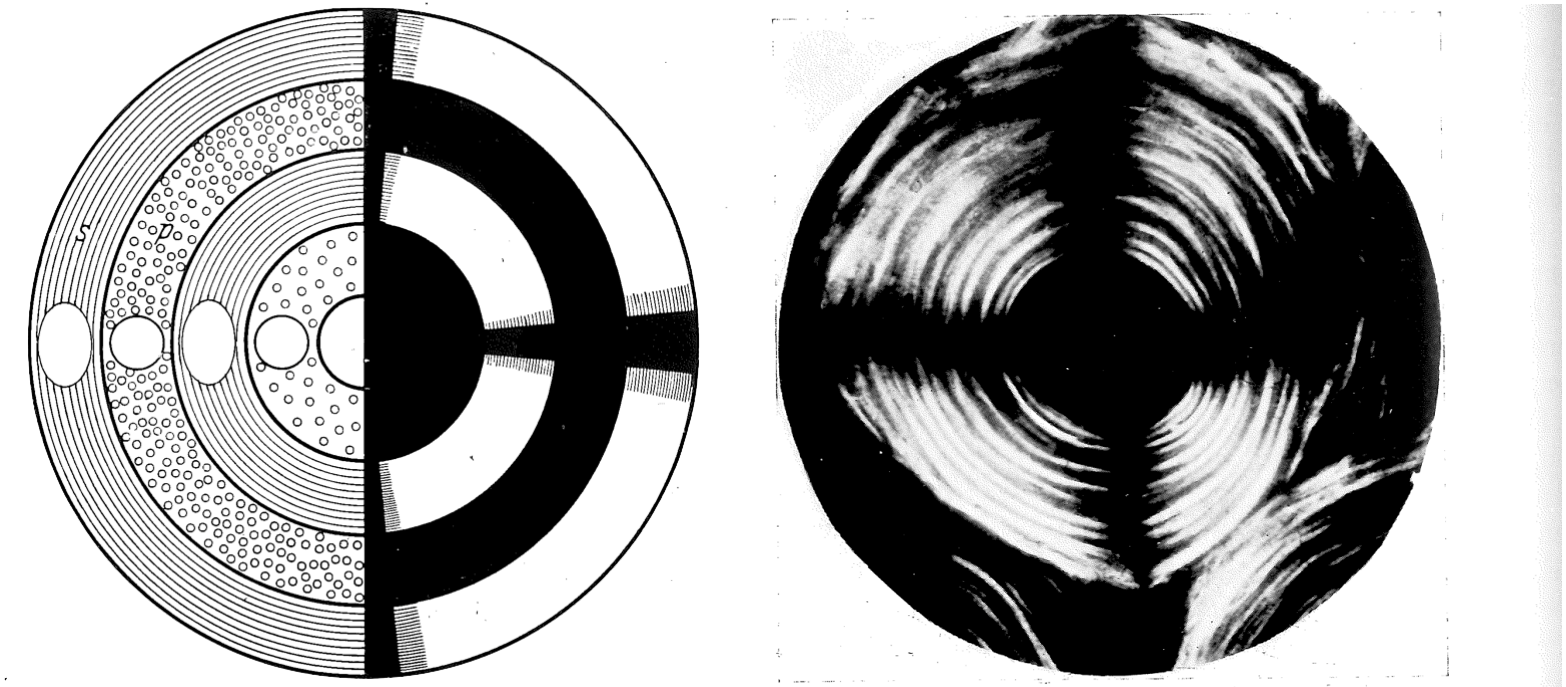


Fig. 223. *Haverss*ches System im Querschliff. Nikols +, 250 : 1.
Nach *W. J. Schmidt*: Arch. exp. Zellf. **2**. 1925, Fig. 5.

Figure 5.2. Schematic (left) and microgram (right; 250:1 magnification between crossed Nicols) of a Haversian system (osteon, a basic unit of bone tissue) from 1934. The schematic diagram indicates the alternating layers of circularly and longitudinally running collagen fibers. In the schematic diagram, the white ovals and circles on the left half indicate anisotropic and isotropic parts, respectively, while the right half indicates what is seen under polarized light. W. J. Schmidt, "Polarisationsoptische Analyse des submikroskopischen Baues von Zellen und Geweben," in *Abderhaldens Handbuch der biologischen Arbeitsmethoden*, Abt. V, Teil 10, 1. Hälfte (Berlin: Urban & Schwarzenberg, 1934), 435–665. (These were figures 222 and 223 in the article.)

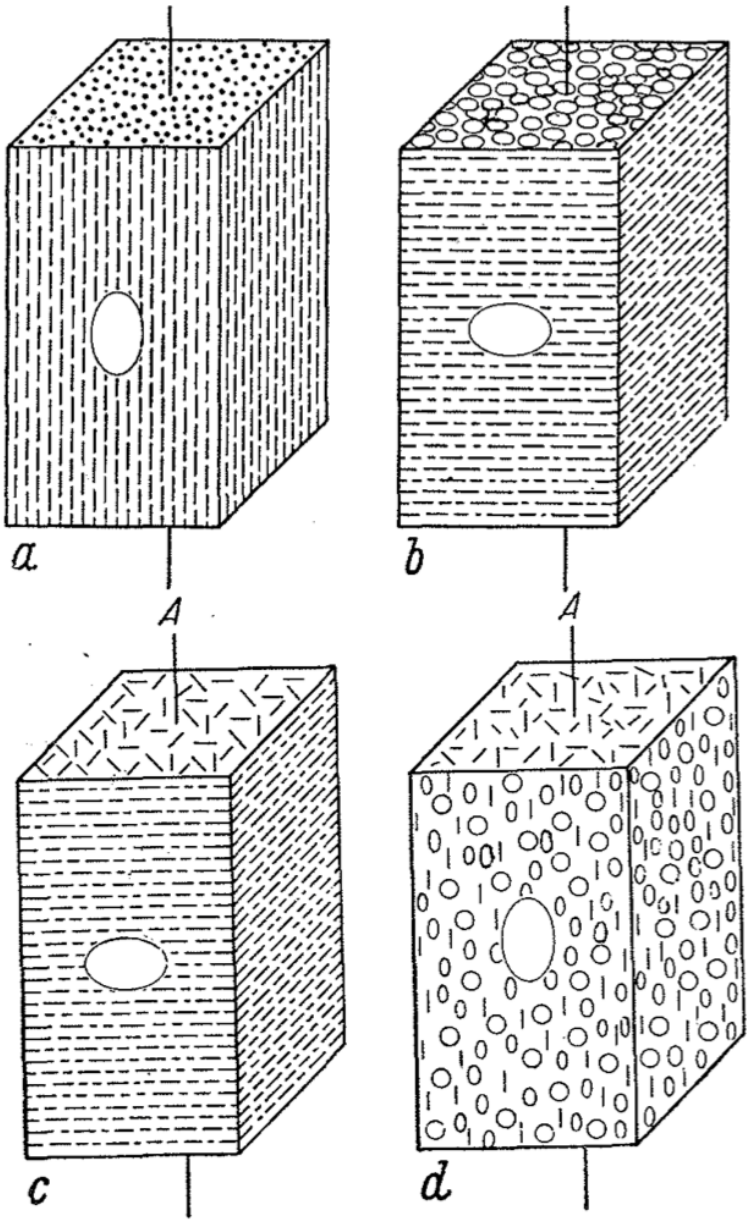


Figure 5.3. Schmidt's reinterpretation of the Wiener mixed-body theory in 1934, trying to represent more complicated, less-idealized systems and align them to expected positive birefringence (vertical index ellipses) and negative birefringence (horizontal index ellipses). *a)* rodlet mixed-body, *b)* platelet mixed-body, *c)* rodlets oriented perpendicular to the orientation axis (*A*), *d)* platelets oriented perpendicular to the orientation axis.

W. J. Schmidt, "Polarisationsoptische Analyse des submikroskopischen Baues von Zellen und Geweben," in *Abderhaldens Handbuch der biologischen Arbeitsmethoden*, Abt. V, Teil 10, 1. Hälfte (Berlin: Urban & Schwarzenberg, 1934), 435–665.

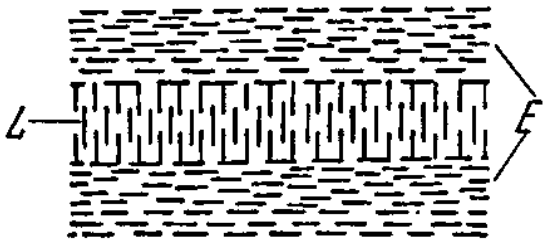


Abb. 20. Schema des Feinbaues der nichtlipoiden Schichten *E* im Außenglied (*L* Lipoidschichten).

Figure 5.4. Schematic diagrams of the micellar structure of the frog eye retina cell, ca. 1935. Left: "Schema of the fine structure of the non-lipoidal layers *E* in the outer member, *L* the lipoid layer." Below: "Possible arrangements of the molecules (*i.e.,* colloid particles) in the surface view of the non-lipoidal layer of the outer member: *a* radial, *b* tangential, *c* disordered arrangement. Note that any of the possibilities for protein structures suggested in the diagram below could fit with the protein structure on the left diagram.

W. J. Schmidt, "Doppelbrechung, Dichroismus, und Feinbau des Aussengliedes der Sehzellen vom Frosch," *Zeitschrift für Zellforschung und mikroskopische Anatomie* 22, no. 4 (1935): 485–522, on 515.

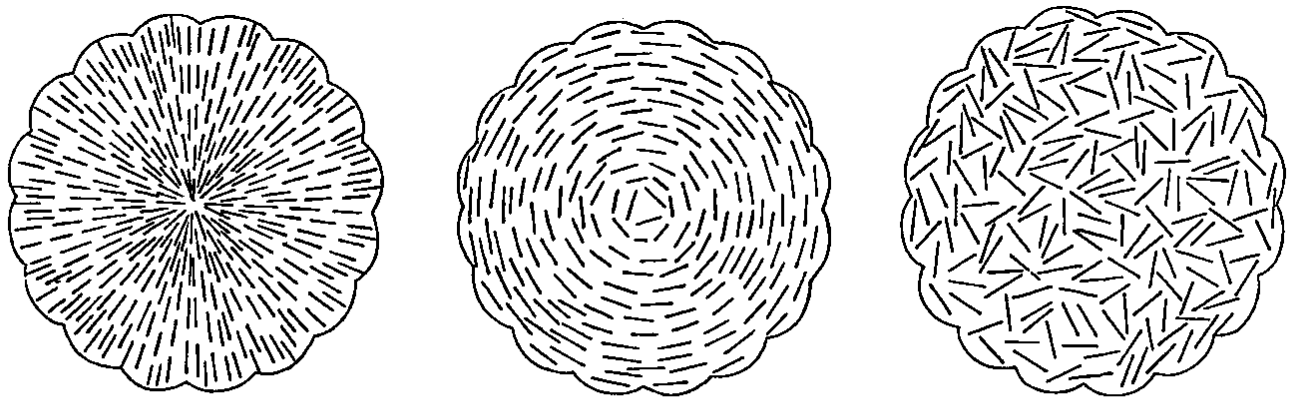


Abb. 21*a*–*c*. Mögliche Anordnungsweisen der Molekeln (bzw. Kolloidteilchen) in der Flächenansicht der nichtlipoiden Schichten des Außengliedes: *a* radiale, *b* tangentiale, *c* regellose Anordnung.

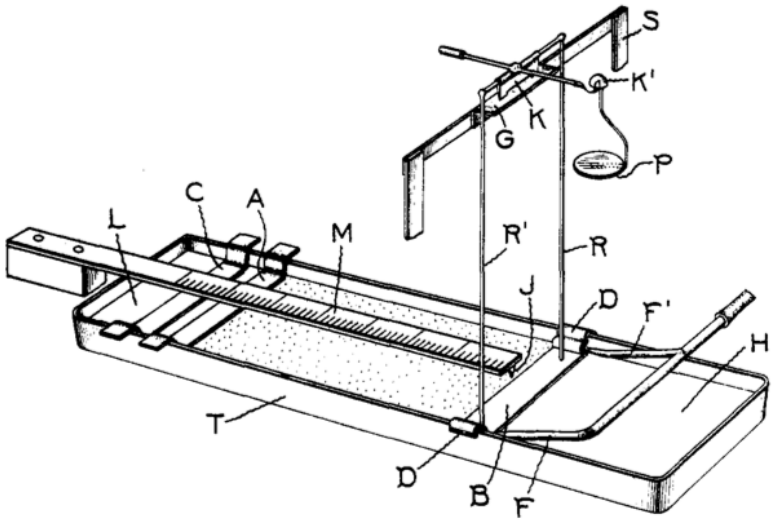


Fig. 6.

Figure 5.5a. Irving Langmuir's modification of the Pockels trough. Irving Langmuir, "The Constitution and Fundamental Properties of Solids and Liquids. II. Liquids.," *Journal of the American Chemical Society* 39, no. 9 (September 1917): 1848–1906.

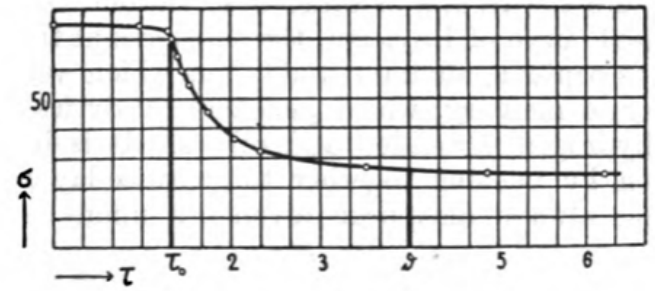


FIG. 65.—Dependence of Surface Tension of Water upon the Thickness of a Layer of Oil upon its Surface.

Figure 5.5b: Non-linear decrease of surface tension (*y* axis) as the amount of oil (*x* axis) increases, as discovered by Pockels in the 1880s. (Graph from Herbert Freundlich, *Colloid & Capillary Chemistry*, trans. H. Stafford Hatfield (New York: E.P. Dutton & Company), 311.

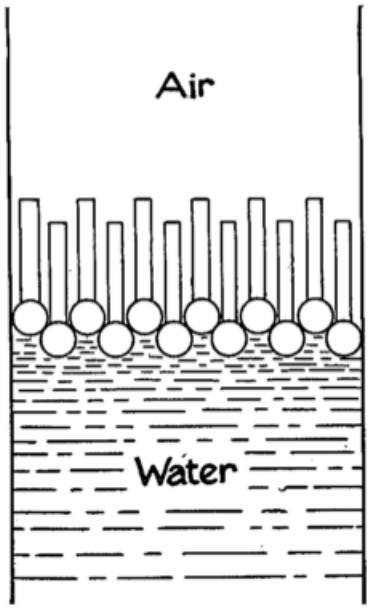


FIG. 1.—Weighted logs floating on water.

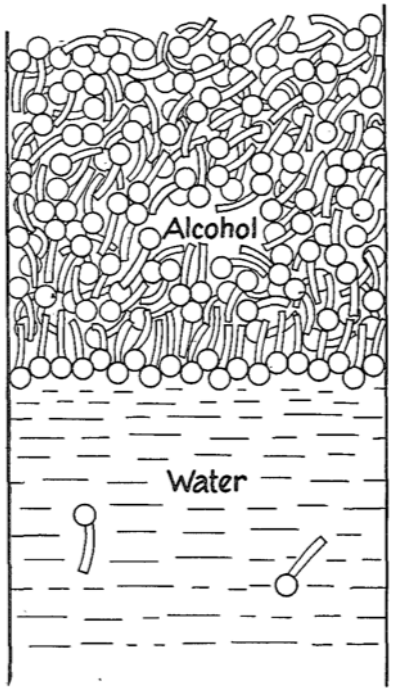


FIG. 9.—Octyl alcohol over water showing orientation of alcohol molecules in the interface.

Figure 5.6. William Harkins' diagrammatic representation of sticks with brass weights on one end, thrown in a container of water. Left: a strictly schematic analogy. Right: introducing an element of realism in a purportedly schematic diagram. William D. Harkins, "The Orientation of Molecules in the Surfaces of Liquids," *Colloid Symposium Monograph* 2 (1924): 141–73.

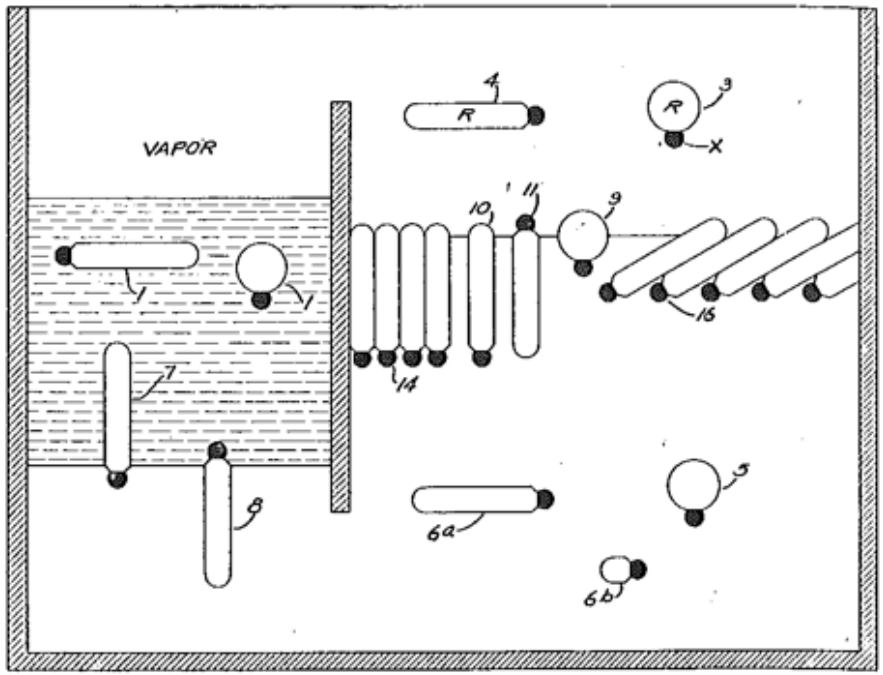


Figure 5.7. Irving Langmuir's diagram explaining "molecular dissymmetry," the small black dots representing a radical active group and the cylinders representing hydrocarbon chains. Irving Langmuir, "The Effects of Molecular Dissymmetry on Properties of Matter," in Colloid Chemistry: Theoretical and Applied, ed. Jerome Alexander (New York: Chemical Catalog Co., 1926), 525–46.

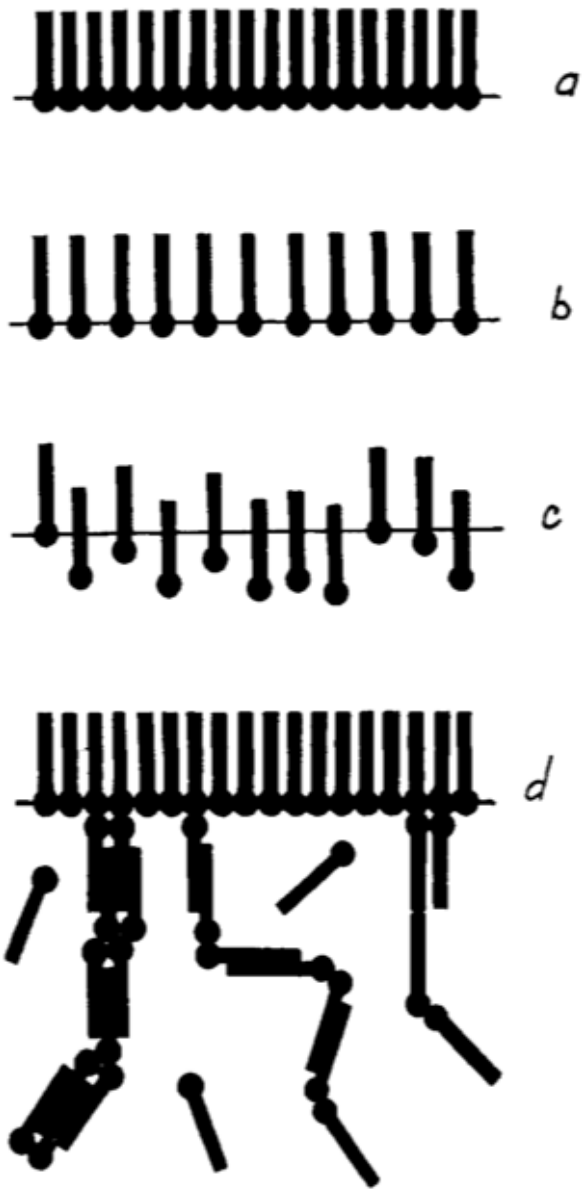


Figure 5.8. Possibly the first time the ball and stick model is used after Harkins? James W. McBain's ball and stick models of monomolecular films, from James W. McBain and George P. Davies, "An Experimental Test of the Gibbs Adsorption Theorem: A Study of the Structure of the Surface of Ordinary Solutions," *Journal of the American Chemical Society* 49, no. 9 (September 1927): 2230–54, doi:10.1021/ja01408a016.

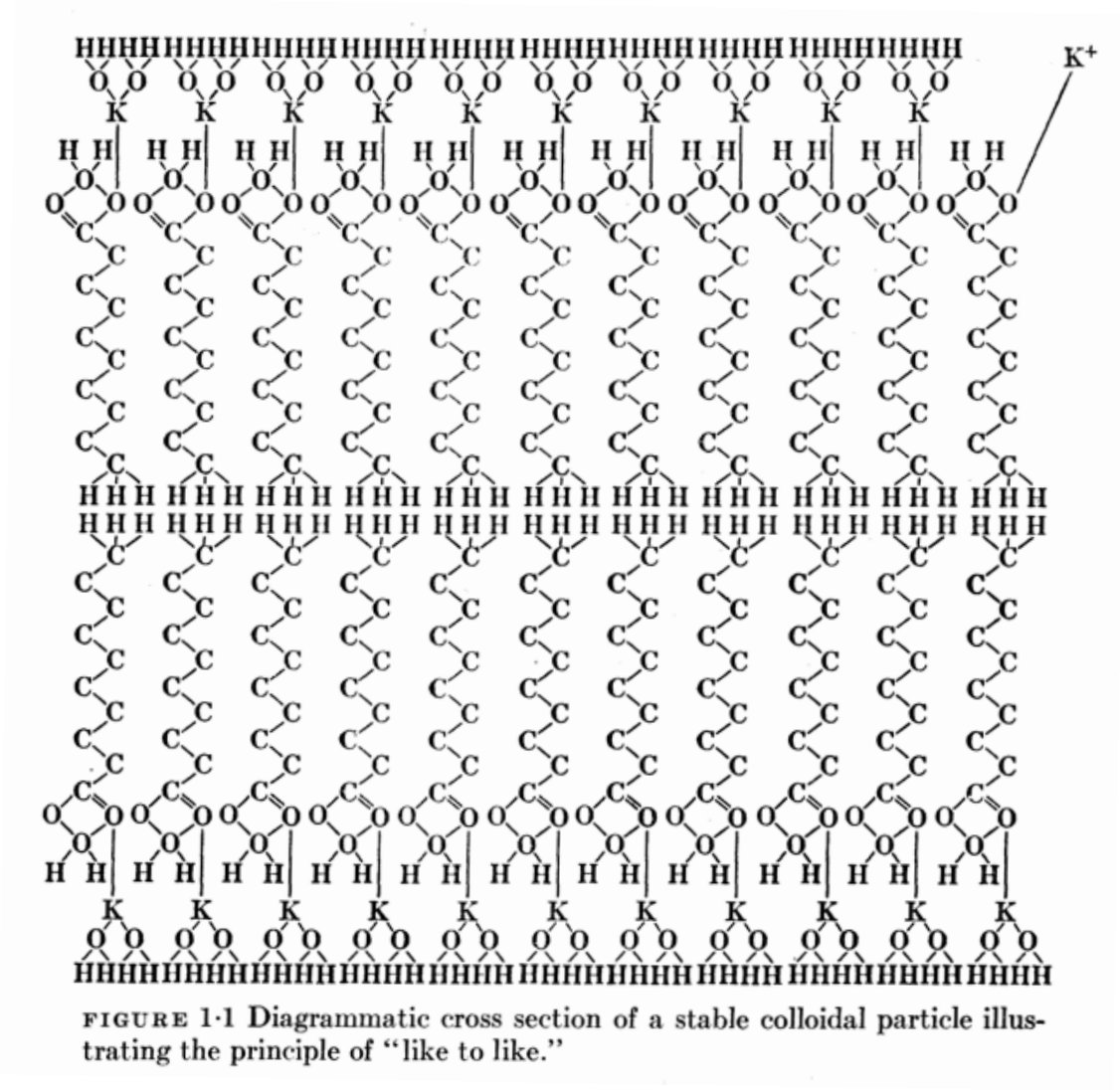


FIGURE 1·1 Diagrammatic cross section of a stable colloidal particle illustrating the principle of "like to like."

Figure 5.9. An overly complicated attempt at chemical realism, the "pair of military hair brushes." This image originally accompanied James McBain's 1925 lecture at the Royal Institution ("Soaps and the Theory of Colloids," *Notices of the Proceedings at the Meetings of the Members of the Royal Institution* 24 (1925): 579–84), but was only printed later in James W. McBain, *Colloid Science* (Boston: Heath, 1950), 5.

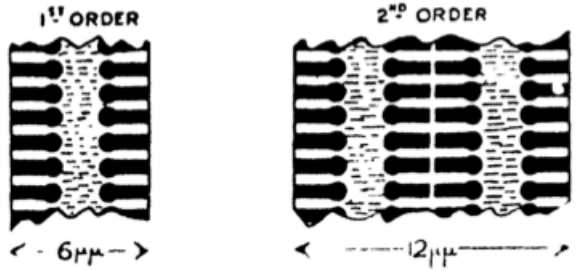


FIG. 59.—Sectional view of black film, diagrammatic.

Figure 5.10. A. S. C. Lawrence's static diagram of very thin soap films, perhaps a first to be shown as a lipid sandwich. This image originally appeared in Lawrence's 1929 booklet *Soap Films: A Study of Molecular Individuality* (G. Bell And Sons, Ltd., 1929), 128; it was reproduced in N. K. Adam's 1930 textbook, *The Physics and Chemistry of Surfaces* (Oxford: Clarendon Press, 1930). 137. (See also Max Stadler, "Assembling Life: Models, the Cell, and the Reformations of Biological Science, 1920-1960" (Ph.D. dissertation, Imperial College, University of London, 2009), 73–74.)

Fig. 4. Raumerfüllung und Anordnung der Atome in einem Kettenstück des Seidenfibroins nach ASTBURY: Stickstoff schwarze, Sauerstoff gestrichelte, Kohlenstoff große, Wasserstoff kleine helle Kreise (nur die vom Beschauer aus sichtbaren Teile des räumlichen Modells sind dargestellt).

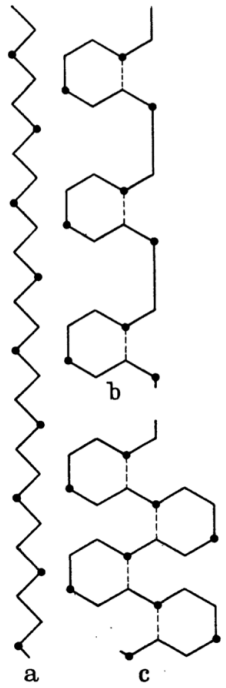


Fig. 5. Das gleiche Kettenstück einer Keratinfadenmolekel in verschiedenem Streckungszustand nach ASTBURY, schematisiert (nur die Stickstoffatome sind in der Fadenmolekel eingetragen): a) β-Keratin (maximale Dehnung), b) α-Keratin (Normalzustand), c) superkontrahiertes Keratin.

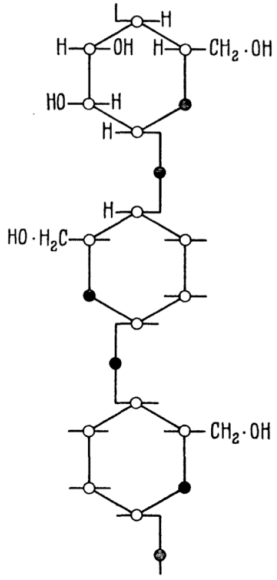


Fig. 7. Kettenstück einer Cellulose (Tunicin)-Fadenmolekel. (Helle Kreise Kohlenstoff, dunkle Sauerstoff.)

Fig. 8. Raumerfüllung und Anordnung der Atome in einem Kettenstück der Cellulose nach ASTBURY. (Sauerstoff gestrichelte, Kohlenstoff große, Wasserstoff kleine helle Kreise.)

Figure 5.11. Schmidt's 1938 *Naturwissenschaften* reproduction of some of W. T. Astbury's diagrams from *Fundamentals of Fibre Structure*: a space-filling model of silk, a model of a keratin fiber in three different states, a chain model of cellulose, and a space-filling model of cellulose. W. J. Schmidt, "Molekulare Bauweisen tierischer Zellen und Gewebe und ihre polarisationsoptische Erforschung," *Naturwissenschaften* 26, no. 30–31 (July and August 1938): 481–90, 509–14.

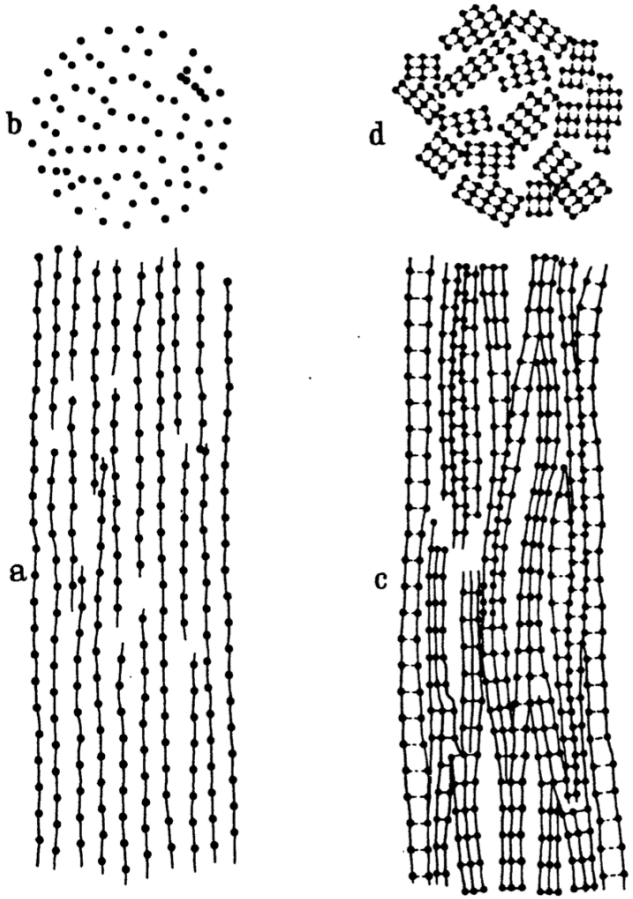


Fig. 12. Schema der fibrillären Bauweise: a) Parallelisierung von Fadenmolekeln, Längsschnitt, b) desgleichen im Querschnitt dargestellt; c) Raumgittermäßige Verknüpfung von Fadenmolekeln (Micellgefüge) im Längsschnitt, d) desgleichen im Querschnitt.

Figure 5.12. Schmidt's revised, chain-molecular diagrams of fiber structure. Left: two kinds of fiber bundles. Below: fibers arranged to create parallel layers, which can be viewed and interpreted from certain angles as either isotropic (from above) or as rodlets (from the sides). W. J. Schmidt, "Molekulare Bauweisen tierischer Zellen und Gewebe und ihre polarisationsoptische Erforschung," *Naturwissenschaften* 26, no. 30–31 (July and August 1938): 481–90, 509–14.

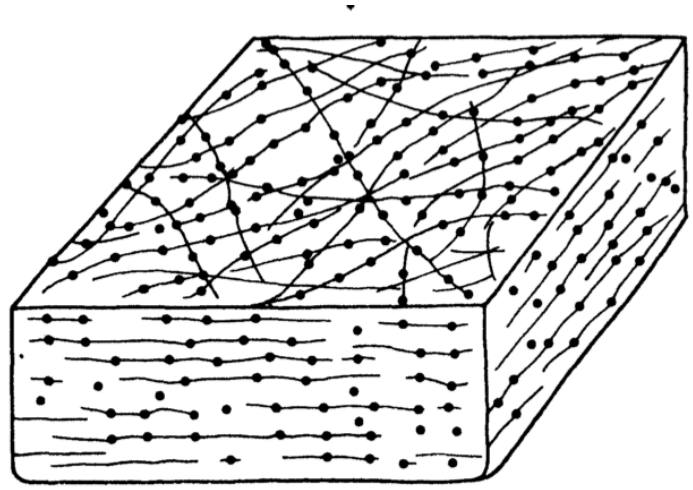


Fig. 13. Schema des Folienbaues.

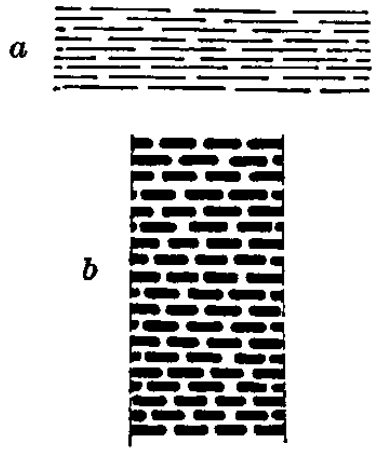


Abb. 22 *a* und *b*. Änderung des Feinbaues der nichtlipoiden Schichten im Außenglied bei thermisch und chemisch ausgelöster Streckung des Stäbchens. *a* Natürliches Verhalten einer nichtlipoiden Schicht, *b* Verhalten nach der Streckung.

Figure 5.13a. Micellar diagram of fiber stretching by heat, ca. 1935: when fiber *a* is stretched vertically, the micelles become wider and shorter. W. J. Schmidt, "Doppelbrechung, Dichroismus, und Feinbau des Aussengliedes der Sehzellen vom Frosch," *Zeitschrift für Zellforschung und mikroskopische Anatomie* 22, no. 4 (1935): 485–522.

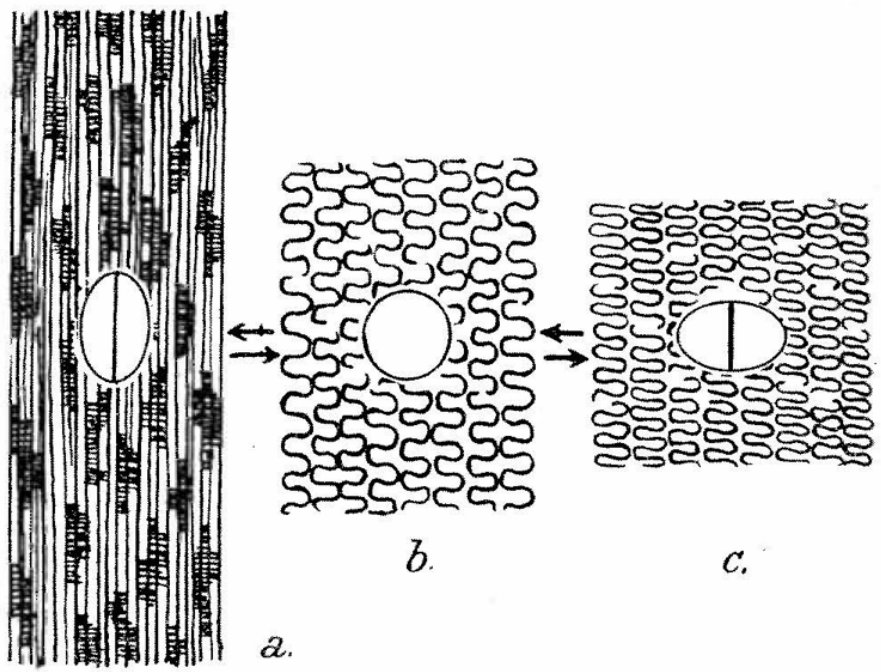


Abb. 52. Reversible thermische Verkürzung eines Elastoidinfadens durch Schmelzen der Kristallite und Schlängelung der Polypeptidmolekeln: *a* = natürlicher positiv doppelbrechender, *b* = isotroper, *c* = negativ doppelbrechender Zustand.

Figure 5.13b. Molecular/chain-molecular diagram of fiber stretching by heat, ca. 1939. Note the change in the sign of birefringence as indicated by the index ellipses, which move from *a)* naturally positively birefringent, to *b)* isotropic, to *c)* a negatively birefringent state. W. J. Schmidt, "Polarisationsoptische Erforschung des submikroskopischen Baues tierischer Zellen und Gewebe: Der experimentelle Weg und einige Beispiele," *Verhandlungen der Deutsche Zoologische Gesellschaft* 41 (1939): 303–89.

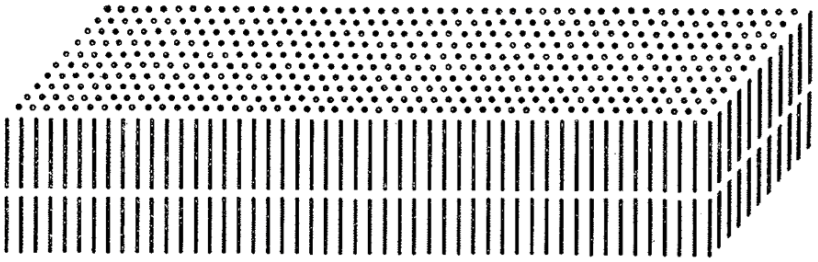


Abb. 17. Schema des molekularen Baues eines Lipoidmicells. (In Anlehnung an P. Thiessen & R. Spychalski, 1931).

Figure 5.14a. Schmidt's 1937 diagram of a static and rigid lipid micelle, taken after Thiessen and Spychalski's x-ray study in 1931. W. J. Schmidt, *Die Doppelbrechung von Karyoplasma, Zytoplasma, und Metaplasma, Protoplasma-Monographien*, bd. 11 (Berlin: Gebrüder Borntraeger, 1937).

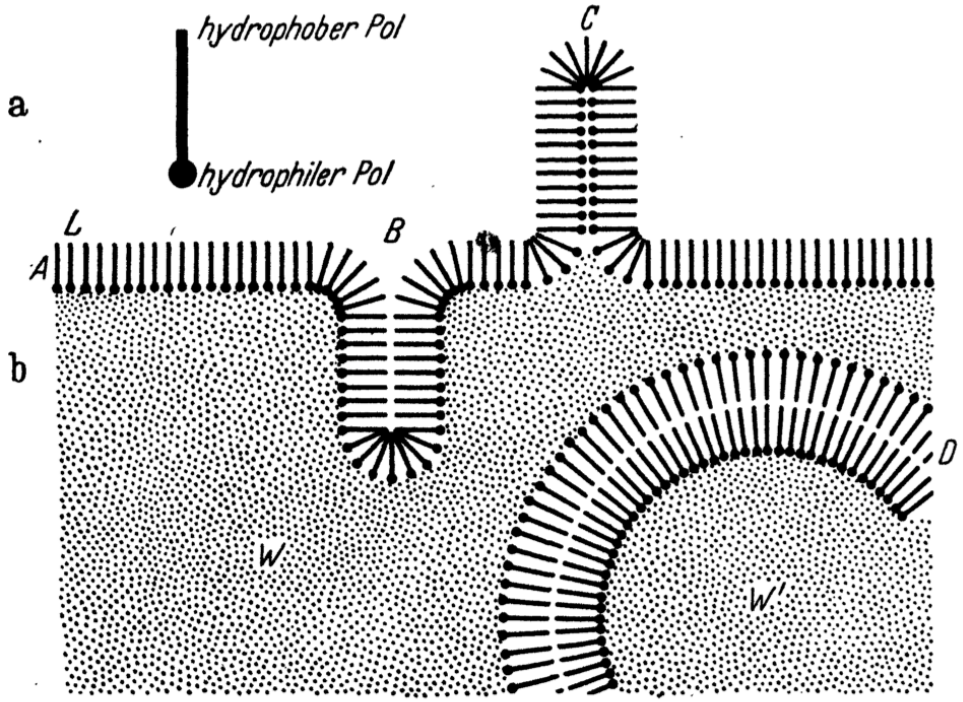


Figure 5.14b. Schmidt's 1938 much more dynamic diagram of lipid molecules, which gives each lipid molecule (*a*) some degree of individuality to form several different kinds of structure. W. J. Schmidt, "Molekulare Bauweisen tierischer Zellen und Gewebe und ihre polarisationsoptische Erforschung," *Naturwissenschaften* 26, no. 30–31 (July and August 1938): 481–90, 509–14.

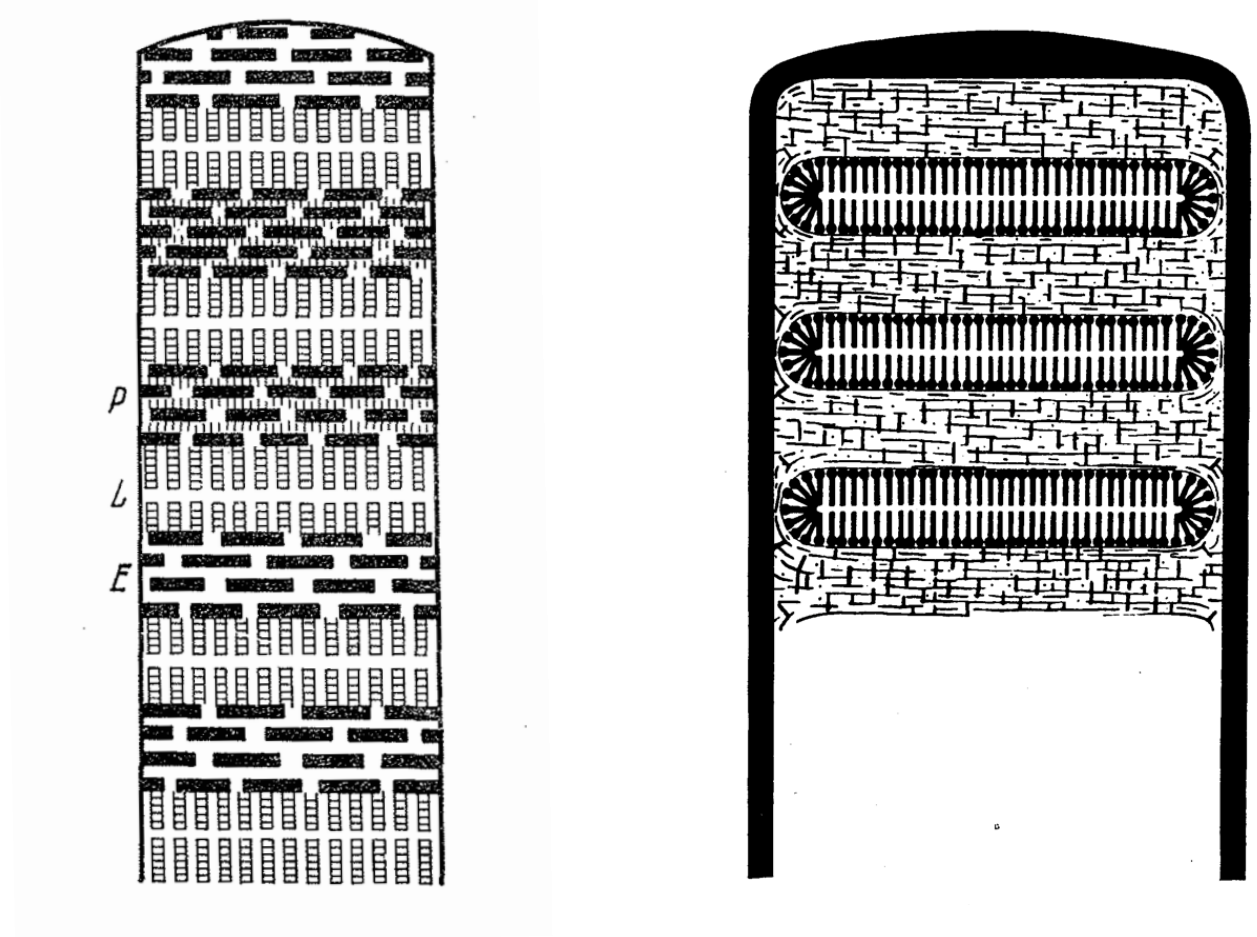


Figure 5.15. Two of Schmidt's diagrams of the frog eye retina protein-lipid system, separated by one year and an entire ontological foundation. The left image is from 1937, showing a micellar, brick-like depiction of proteins (*E* and *P*) and lipid (*L*). The right diagram is from 1938, showing a dramatic change how both the protein and lipid layers are drawn — the former as a fibrous network, the latter as an orderly bilayer. W. J. Schmidt, *Die Doppelbrechung von Karyoplasma, Zytoplasma, und Metaplasma*, Protoplasma-Monographien, bd. 11 (Berlin: Gebrüder Borntraeger, 1937); and W. J. Schmidt, "Polarisationsoptische Analyse eines Eiweiß-Lipoid-Systems, erläutert am Außenglied der Sehzellen," *Kolloid-Zeitschrift* 85, no. 2/3 (1938): 137–48.

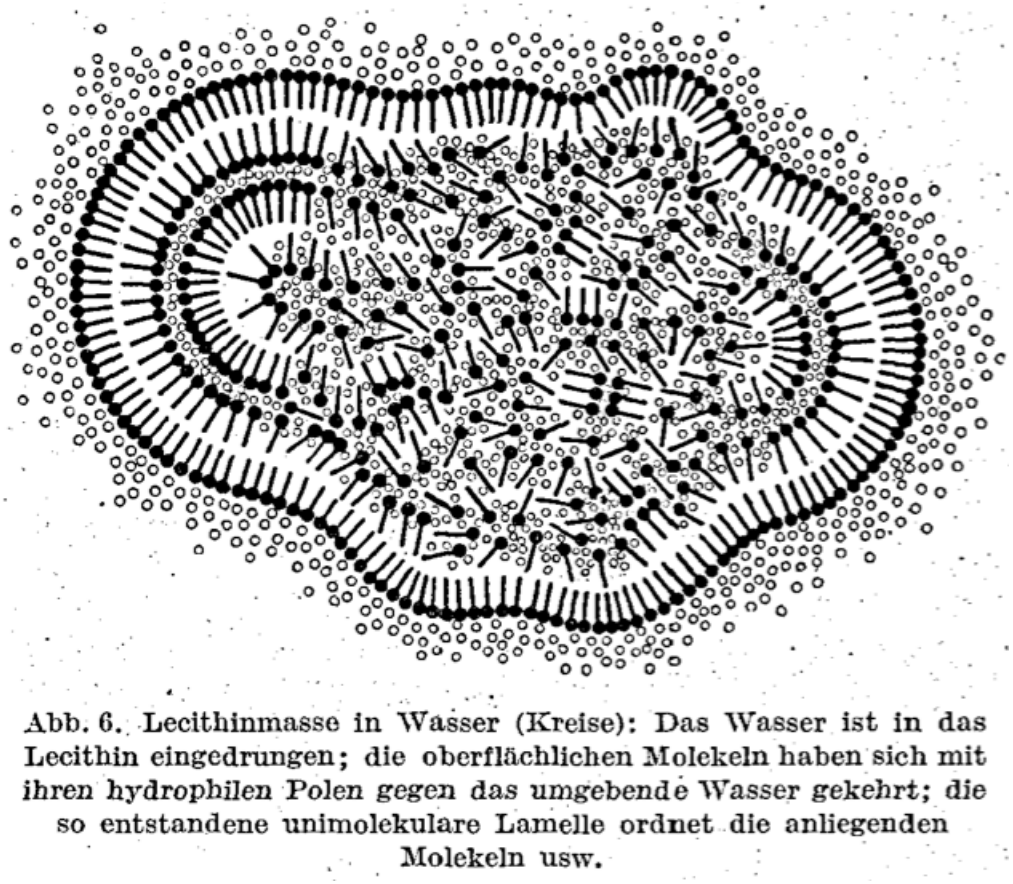


Abb. 6. Lecithinmasse in Wasser (Kreise): Das Wasser ist in das Lecithin eingedrungen; die oberflächlichen Molekeln haben sich mit ihren hydrophilen Polen gegen das umgebende Wasser gekehrt; die so entstandene unimolekulare Lamelle ordnet die anliegenden Molekeln usw.

Figure 5.16. Wilhelm Schmidt's realistic diagrammatic image of a cross section of a lecithin droplet in water. "The water has invaded the lecithin; the outer surface molecules have turned against the surrounding water with their hydrophilic poles; the developing unimolecular lamella arranges the adjacent molecules, and so on." W. J. Schmidt, "Die Doppelbrechung des Protoplasmas und ihre Bedeutung für die Erforschung seines submikroskopischen Baues," *Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie* 44, no. 1 (December, 1941): 27–95.

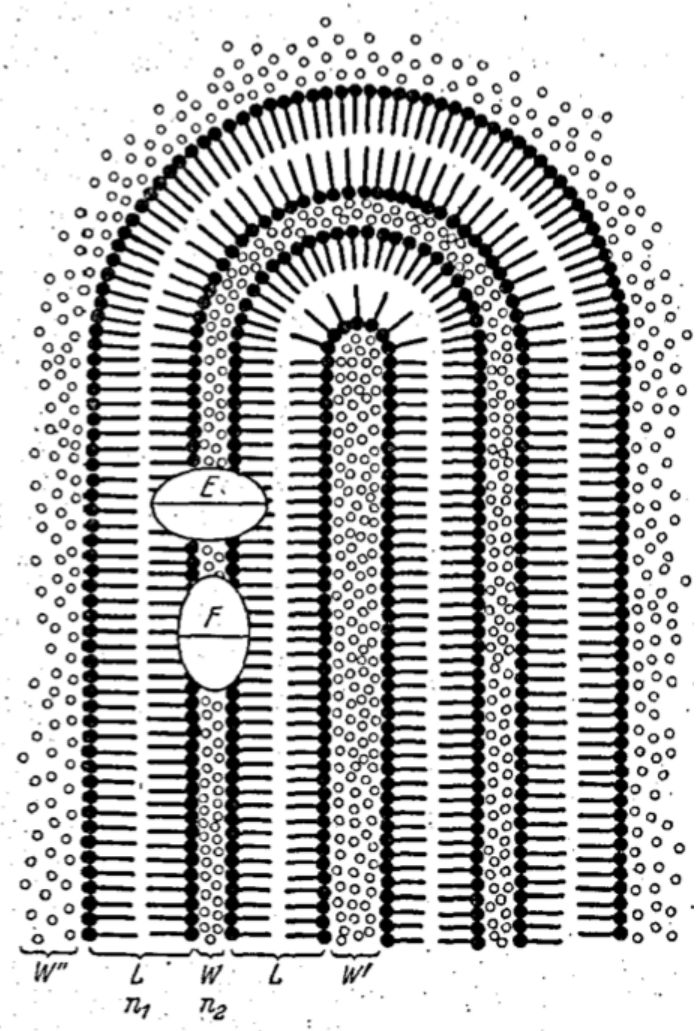


Abb. 7. Feinbau und Optik eines *Myelinschlauches* (oben das freie Ende) am Längsschnitt: *L* bimolekulare Lamelle des Lipoids mit der Brechzahl n_1; *W* Wasserschicht mit der Brechzahl n_2; *W'* axialer Wasserfaden; *W''* umgebendes Wasser. *E* Eigen-, *F* Formdoppelbrechung.

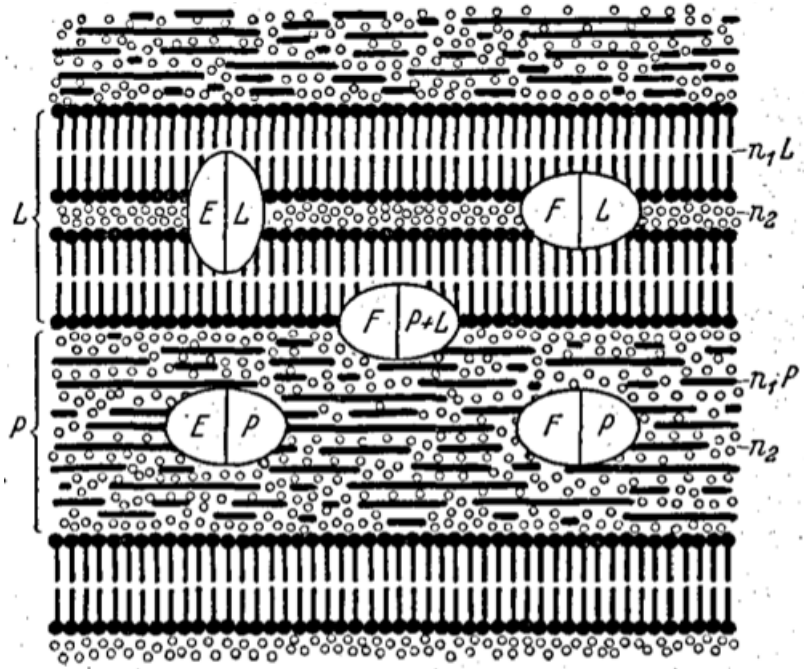


Abb. 8. Feinbau und Optik eines *Schichtsystems* aus *Proteinfolien* (*P*) und *bimolekularen Lipoidlamellen* (*L*) am Durchschnitt. *EP* Eigen-, *FP* Formdoppelbrechung des Proteins; *EL* Eigen-, *FL* Formdoppelbrechung des Lipoids; *F*: *P* + *L* Formdoppelbrechung des Protein-Lipoid-Schichtkörpers; $n_1 P$ Brechzahl des Proteins; $n_1 L$ Brechzahl des Lipoids; n_2 Brechzahl der Zwischenmasse (Wasser).

Figure 5.17. Schmidt's diagrams of the myelin tube/figure and a layered lipid-protein system in cross-section. Note the optical index-ellipses on both diagrams, which indicate the kind of form (F) and intrinsic (E) birefringence characteristics one should expect from such a system. Such expectations would only be possible if these diagrams were conceived as realistic representations of the biological microworld. "Die Doppelbrechung des Protoplasmas und ihre Bedeutung für die Erforschung seines submikroskopischen Baues," *Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie* 44, no. 1 (December, 1941): 27–95.

Fig. AA: "Adult compact bone viewed by partly crossed transmitted polarized light with a 530nm tint plate." Photo by Jeffrey Kerr, The Royal Photographic Society © 2016, http://rps-science.org/events/International-Images-for-Science/photographer/image/2180/

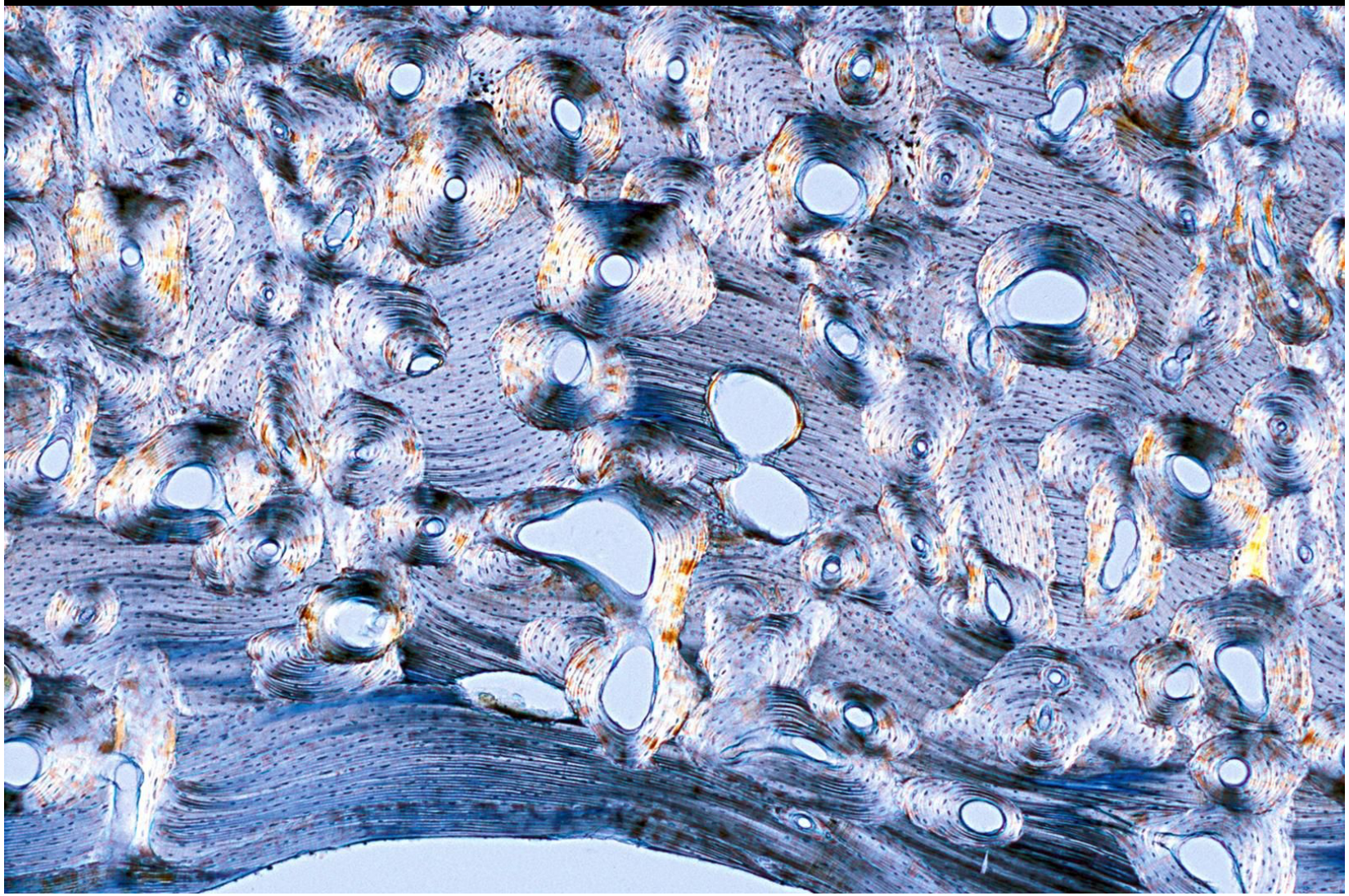
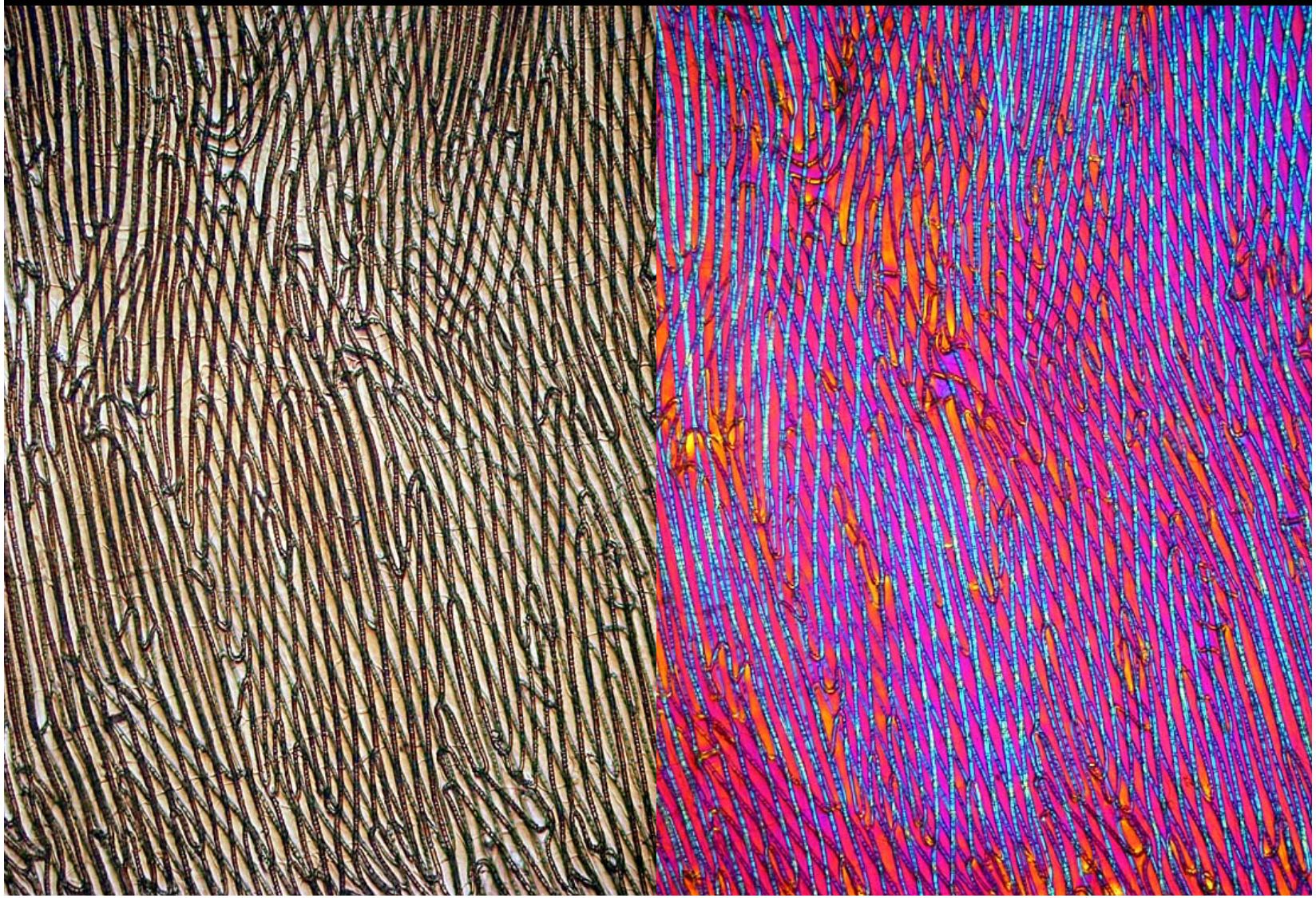


Fig. BB: *Lunaria annua* pod husk. Left: viewed under ordinary light. Right: viewed in cross-polarized light. 100x. Micrograms by Phil Gates, http://beyondthehumaneye.blogspot.com/2010_12_01_archive.html



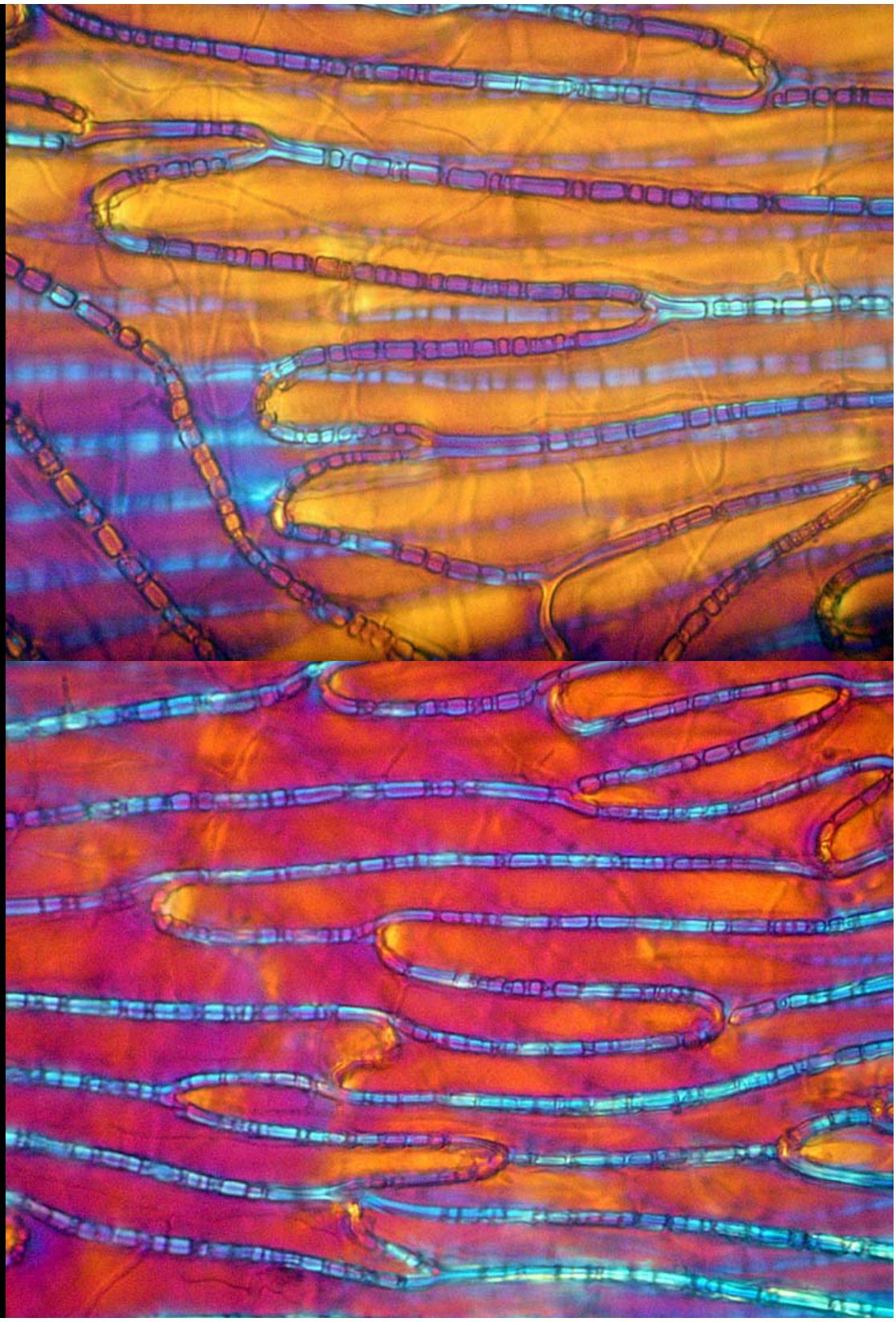


Fig. CC: *Lunaria annua* pod husk, 400x, under crossed polarizers. The different colors in the micrograph on the right comes from being oriented differently with respect to the axes of the crossed polarizers; this highlights different parts of the cell wall structure. Microgrames by Phil Gates, http://beyondthehumaneye.blogspot.com/2010_12_01_archive.html

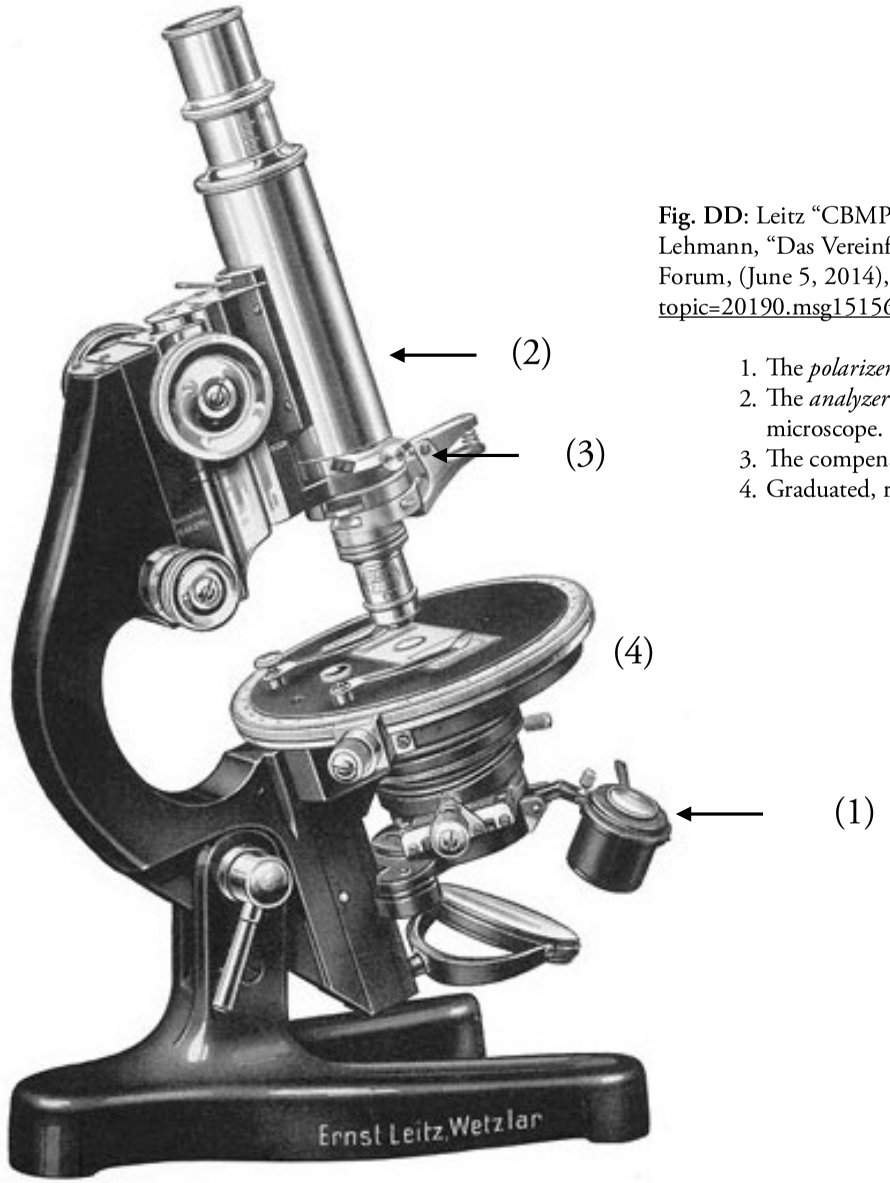


Fig. DD: Leitz "CBMP" polarized light microscope, ca. 1931. (Scan from Wolfgang Lehmann, "Das Vereinfachte Universalmikroskop CBMP von Leitz," forum post, Mikro-Forum, (June 5, 2014), http://www.mikroskopie-forum.de/index.php?topic=20190.msg151563.

1. The *polarizer* Nicol prism, here swung out.
2. The *analyzer* Nicol prism is inserted in a square opening on the left side of the microscope.
3. The compensator is inserted in this narrow slot, below the analyzer.
4. Graduated, rotating stage.

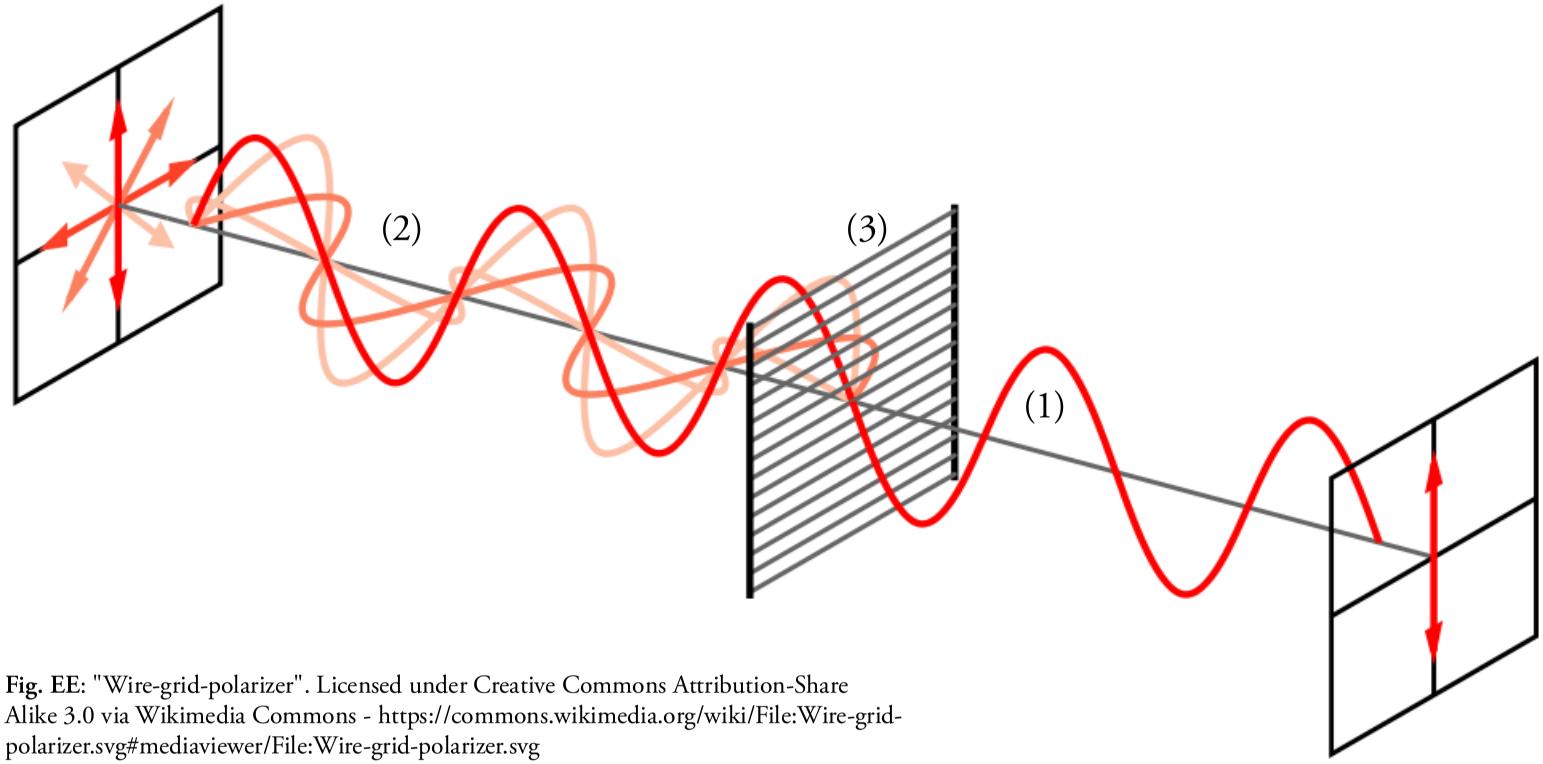
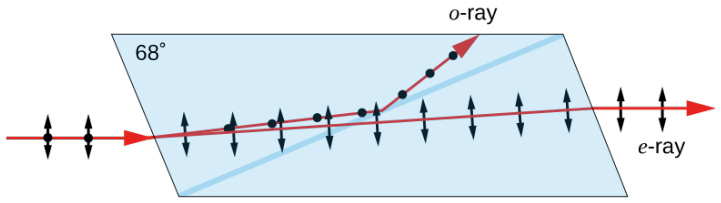


Fig. EE: "Wire-grid-polarizer". Licensed under Creative Commons Attribution-Share Alike 3.0 via Wikimedia Commons - https://commons.wikimedia.org/wiki/File:Wire-grid-polarizer.svg#mediaviewer/File:Wire-grid-polarizer.svg

1. Plane polarized light
2. Ordinary, unpolarized light
3. Wire grid polarizer



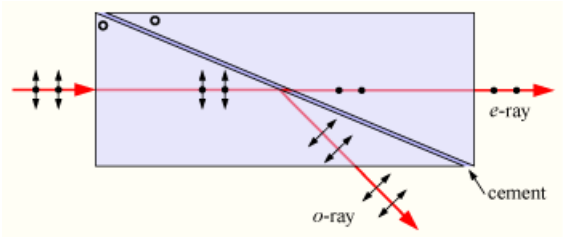


Figure FF: Above: Nicol prism. Below: Glan-Thomson prism.

Nicol prism diagram by: By Fred the Oyster, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=35266026

Glan-Thomson prism, (CC BY-SA 3.0), https://en.wikipedia.org/wiki/File:Glan-thompson.png