HEADS AND TAILS

MOLECULAR IMAGINATION AND THE LIPID BILAYER, 1917–1941

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That the cell has a membrane is perhaps one of its most obvious features: more than any other part, the membrane defines the cell, sets its outer boundary, and determines how the cell as an individualized unit interacts with its environment. A schematic picture of the cell membrane is a staple of any introductory biology textbook, in part because it does more than any other illustration to show that cells can be pictured as being composed of molecules large and small, with all manner of shapes and functions, a complex sandwich of lipids, studded with potato-like protein globules and wispy carbohydrate chains. The membrane binds the cell into a single entity, and today it is almost impossible to imagine that anyone could have doubted its existence.

Yet until the late 1910s the existence of the cell membrane was a matter of considerable debate and controversy, and even Edmund Cowdry's *General Cytology* in 1924 had a few hints of ambiguity and doubt regarding the cell membrane's existence and composition. An early chapter by Albert Mathews cheerfully suggested that "limiting membranes wherever they occur" might be made of oriented graphite rods, a suggestion made largely through his idiosyncratic analogy to electric battery construction (Cowdry 1924, 43, 68–71).[1] Merle Jacobs's chapter on cell permeability spent several pages defending the existence of a cell membrane that could allow for differential diffusion, yet he also noted a great deal of disagreement about the membrane's composition, writing that "the whole subject is of too speculative a nature to make further discussion profitable; . . . what is most needed in the field of cell permeability at the present day is facts" (156).[2] Robert Chambers even briefly noted the possibility that some cells might not possess a membrane, but have instead a thick, "cement-like substance" holding cells together in some tissues (241). If Cowdry and his collaborators were largely convinced of the reality of the cell membrane, in 1924 it would still have been a relatively novel and fraught position to take, and any theory of the membrane's structure would have remained entirely a matter of speculation.

By the 1930s, however, the membrane was not only a positive fact of science, but the idea that it primarily consisted of a lipid bilayer and associated proteins was quickly accepted as a likely molecular structure for the cell membrane. The so-called Danielli-Davson model of the cell membrane from 1935 is now often cited as the first time a lipid bilayer was proposed as the basic structural element of the cell membrane, though James Danielli (1911–1984) found this attribution irritating. The bilayer concept has also often been attributed to Evert Gorter and François Grendel's 1925 paper, "On Bimolecular Layers of Lipoids on the Chromocytes of the Blood." It appears that Gorter and Grendel's membrane hypothesis was not well known until the late 1930s, by which time Danielli's theory had achieved broad recognition, and credit was retroactively given (Lombard 2014, 10–11). At least later in life, Danielli stressed that the lipid bilayer was *not* his idea, and 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 (Danielli 1973, 64). Indeed he and his colleague Hugh Davson never explained why they thought the cell membrane had a lipid bilayer at all; since the lipid bilayer was so obvious, their attention was on the permeability of the protein layer they thought was adsorbed on either side of the lipid (fig. 10.1; Danielli and Davson 1935). Danielli's later irritation might have come from the fact that he and Davson were trying to articulate a functional or physiological theory of cell permeability, but were misread as having "discovered" a biological-structural principle that they claimed no credit for.

How was it decided that the cell's membrane and interior lamellar structures were composed of phospholipids, arranged with their heads facing outwards and tails facing inwards? And how did such structure go from an unprofitable speculation in 1924 to an obvious matter of fact in 1935? In this chapter I argue that many biologists arrived at the lipid bilayer structure largely through a schematic, graphical iconography, one that was originally developed as a strictly heuristic analogy or conceptual aid for the abstract physical concept of *molecular orientation*. 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

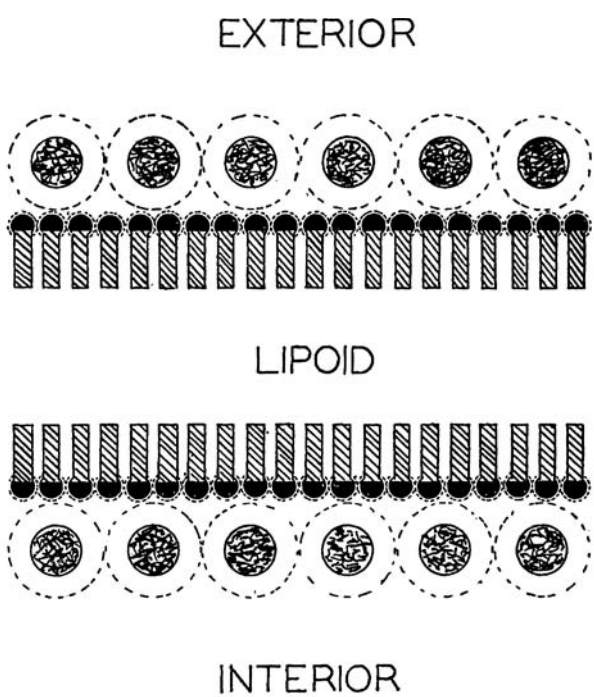

Fig. 1 Schema of molecular conditions at the cell surface.

Figure 10.1. Danielli-Davson model of the cell membrane, "of between unimolecular and trimolecular thickness," with spherical protein molecules adsorbed to both surfaces. Reprinted from Danielli and Davson 1935, 498. With permission of John Wiley and Sons.

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 submicroscopic atoms, molecules, and otherwise invisible particles and forces. Ursula Klein (2003) and David Kaiser (2005) have each argued that "paper tools," mathematical symbols, diagrams, and even doodles can play a part in directing and keeping account of unruly and abstract scientific thought. And building upon the work of Klein and Kaiser, Alan Rocke (2010) 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 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 pale shadows of scientists' dreams and flights of fancy about the microworld—dreams and images that are often not condoned in "proper" scientific settings like scholarly journals or monographs. In this chapter I take a more limited approach to 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.

Here I 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. 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 suspicion, as many have noticed slippage between actors' and analysts' use of the words *model* and *modeling* (Creager, Lunbeck, and Wise 2007; de Chadarevian and Hopwood 2004). Didactic genres of scientific writing carry the weight of intentional transmission and translation, and I would like to entertain the idea that images and analogies are among the more potent and portable parts 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. I argue that in the 1920s and 1930s, the cell membrane and especially the "molecule" were precisely such underdetermined concepts, for which these kinds of translations between disciplines could happen without any clearer pattern of citation or other historically traceable intellectual descent.

More specifically in this chapter I seek to show how the concept of molecular orientation emerged out of physical chemistry in the 1910s and transformed from a relatively difficult synthesis of mathematical models, empirical facts, and abstract physical theories to an easily manipulated image or icon on paper and in the imagination. By looking for the graphical

and imaginary origins of the lipid bilayer in biology, I show how the lipid bilayer became "obvious" to a small number of biologists in the mid-1930s. One of these biologists, the Giessen zoologist Wilhelm J. Schmidt (1884–1974), went further than most, imagining and then mobilizing the image of self-orienting lipids to render a dazzling world of submicroscopic atoms and molecules, all delicately assembled through no forces foreign to physics and chemistry.

The "Molecule" up to 1924

The word *molecule* itself was an underdetermined concept in the nineteenth century, despite its common use, and it was only in the years after World War I that the molecule was clearly conceived as an assemblage of atoms with definite shape.[3] 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" (OED Online, s.v. "molecule"). Even a century and a half later, Cartesian vortex theory could still be deployed in biology and natural history, with little change to the neo-Epicurean meaning of the word *molecule*: for example, "Life, then, 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 [*les molécules individuelles*] are continually entering, and from which they are constantly departing" (Cuvier 1817, 13).

If corpuscular and discontinuous theories of matter had little bearing on biology in the nineteenth century, it was perhaps in part due 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 (Schütt 2002; Gavroglou and Simões 2012). Even if chemists were essentially united in a practical or pragmatic understanding of molecular *identity* by the 1860s—that is, 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 merely formulaic conventions on paper alone (Nye 1972; Nye 1993; Nye 1996; Ramberg 2003; Rocke 2010). 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 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" (Maxwell 1868, 136). 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 (Porter 1994; Staley 2008). 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 (Gray 1931, 14).

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 physicists' attempts to quantify both surface tension and molecular dimensions. Quite famously, in the early 1880s, while caring for convalescent parents, 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 meat extract and her father's pharmaceutical balance, 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 the degree of contamination adjustable by a long tin or paper strip that scraped the water's surface, stretching or compressing the oil slick (Al-Shamery 2011; Beisswanger 1991; Rayleigh 1899; Ostwald 1932).

Meanwhile, in 1889 Lord Rayleigh (John William 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 at home with his wife, Evelyn Balfour (Opitz 2012), drew a bath thirty-three inches in diameter and placed camphor flakes on the surface; then, using a loop

of platinum wire, he deposited tiny amounts of olive oil, which he claimed to be able to measure down to a twentieth of a milligram (Rayleigh 1890). 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 ($\mu\mu$ in late nineteenth-century notation)—and, by extension, that this measurement might estimate the diameter of a single molecule of olive oil. By January 1891, Pockels had read of his interest in thin oil films in the *Naturwissenschaftliche Rundschau*, and wrote a twelve-page letter to Rayleigh, describing her tin trough apparatus and the variability of the surface tension of contaminated water. Rayleigh immediately forwarded the letter to *Nature* for publication, securing Pockels's high standing among physicists (Pockels 1891; Al-Shamery 2011).

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: in France, for example, Henri Devaux performed research on the camphor point, surface tension, and molecular diameters with a tiny toy boat (Devaux 1888; Devaux 1913). What they had in common, however, was a continuing operative assumption that molecules were perfect spheres—after all, this is the only way one could assume a molecule has a diameter, rather than a length, width, and height (Garber 1978). The physical assumption of spherical molecules in turn affected the way Rayleigh interpreted Pockels's 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. 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 of packing the spherical molecules in an increasingly tight space, as well as the different forces at work between the 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 (Rayleigh 1899, 337).

Interpreting Surface Tension: Molecular Orientation

It was this confluence of the clear facts of surface tension measurements and the tentativeness of molecular hypotheses that would lead two different American physical chemists to independently and simultaneously develop the theory of molecular orientation in 1917.[4] 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 (Coffey 2008, 128–34).[5] Even though Harkins and Langmuir eventually 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 (Süsskind 2008; Kohler 1974). 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 light bulb design (Wise 1980; Wise 1983; Reich 1983). His most important agenda in the 1910s and 1920s 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. The experiments of Rayleigh and Pockels with oil films provided the opportunity to build that bridge.

Langmuir (1917) used what was essentially a more elaborate version of Pockels's tin trough, repeating many of Pockels's and Rayleigh's experiments on surface tension. The key difference was that Langmuir used very specific and chemically pure oils, rather than whatever 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 this ability to lower surface tension with uncompressed films 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.[6] 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.[7] 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 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's 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, the theory suggested that urea and water enter into solution very easily because they have extremely low surface tension, while oil and water are so insoluble you can see the surface tension working with your 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. Using a much more precise set of instruments than the Pockels-Langmuir

trough (Harkins and Brown 1916; Harkins and Humphery 1916), Harkins's team surveyed surface tension data for 336 different substances in both air and 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 (Harkins, Brown, and Davies 1917; Harkins, Davies, and Clark 1917). 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?

> 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 . . . since the surface tension of water at 20° is, according to our measurements, 72.8 dynes per cm., the free energy per square cm. is 72.8 ergs. The total energy of the two surfaces, each of which may now be supposed to have an area of 1 square cm., will be 145.6 ergs. 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. (Harkins, Brown, and Davies 1917, 335)

Or, stated in more formal terms: If the independent surfaces of two separate substances are maintained by a certain amount of energy, then what is the decrease in energy if two substances approach and touch one another? This gave the following mathematical expression:

$$(\gamma_a + \gamma_b - \gamma_{ab} = -\Delta\gamma),$$

where γ_a and γ_b are the surface tension measurements of substances *a* and *b* independently in air or water, and γ_{ab} is the surface tension of *a* and *b* when they are in contact with each other. If there is difference remaining, $-\Delta\gamma$, it would suggest that there is something about the interface of the two liquids that is 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" (363). Harkins's 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: there must be some shape, or structure, or other kind of polarity in molecules that causes them to orient at the interface, and this orientation works to reduce surface tension.

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's writings and lectures were only slightly less difficult, but he was to prove more capable than Langmuir in 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 interests and concerns of colloid chemistry. In the 1920s colloid chemistry was a discipline ascendant, propelled by effective evangelists, promises of wide industrial application, and catholic epistemological standards (Ede 2007, 78–101). Colloids were defined from the mid-nineteenth century as heterogeneous aggregates that defied the usual methods of chemical analysis by sublimation or crystallization; colloid chemistry was thus a science of unruly and mixed materials like soaps, blood, rubber, soil, mucus, sewage, and, crucially, cells and protoplasm.

Colloid chemistry was typically instrumentalist or nominalist in its methods, in large part because of the wide range of materials classified as "colloids"; 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. This focus on techniques of measurement and description of materials at hand allowed colloid chemists to communicate across vastly different specialties, despite

working with a diverse range of colloidal materials. John Heilbron (1982), Ted Porter (1994), and others have called this general tendency in fin de siècle physics "descriptionism," and Porter in particular has argued that this epistemological remove from specific objects of inquiry allowed physics to broaden its scope and influence—that "descriptionism aimed to make physics almost impregnable, to confer on it 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" (Porter 1994, 130). 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.

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.[8] Harkins's lecture, "The Orientation of Molecules in the Surfaces of Liquids," has 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: "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" (Harkins 1924b, 141).

This exercise in imagination was then accompanied by a visual and 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.) (Harkins 1924b, 141–42)

The first figure in the lecture is static (fig. 10.2*A*), and claims to represent the analogy of weighted logs floating on water.

By equal measure, Harkins also emphasized that his diagrams were "highly conventionalized" (Harkins 1924b, 149), and in some of them it is not clear whether the diagrams were supposed to illustrate the molecules themselves or to illustrate dissymmetrical fields of molecular and surface forces. Yet the potential for slippage into realism was clear, and some of Harkins's other figures (fig. 10.2*B*) 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's 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, Harkins managed to produce schematic diagrams that were realistically suggestive precisely because of their liveliness.

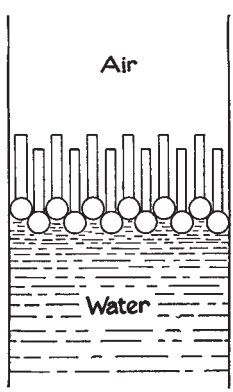

FIG. 1.—Weighted logs floating on water.

A

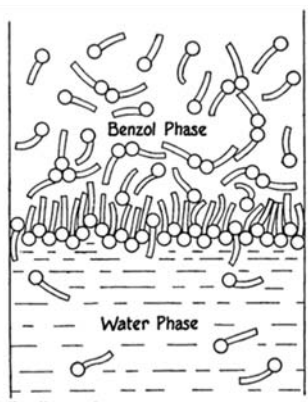

FIG. 3.—Butyric acid distributed between water, benzol and the interface between the two.

B

Figure 10.2. William Harkins's diagrammatic representation of sticks with brass weights on one end, thrown in a container of water. *A*, a strictly schematic analogy. *B*, introducing an element of realism in a purportedly schematic diagram. From Harkins 1924b, 142, 151.

It is not clear exactly how or when Harkins's diagrams began to make 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 Harkins even mentions that polar molecules "have been represented in this laboratory for many years" by the ball-and-stick symbol (Harkins 1924a, 154), though this is the only place where he makes this claim. (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 multivolume 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" (Alexander 1926, 192–264). Langmuir as well wrote a chapter for Jerome Alexander's textbook (525–46), 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's 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 (fig. 10.3). 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 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 a vast number and amount of surfaces. 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).[9] 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 thus have an exterior surface that remained in contact with the continuous phase, and with the total surface between the two phases measurable in the range of tens to hundreds of square meters within a single cubic centimeter of a colloid substance (Freundlich 1907). 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

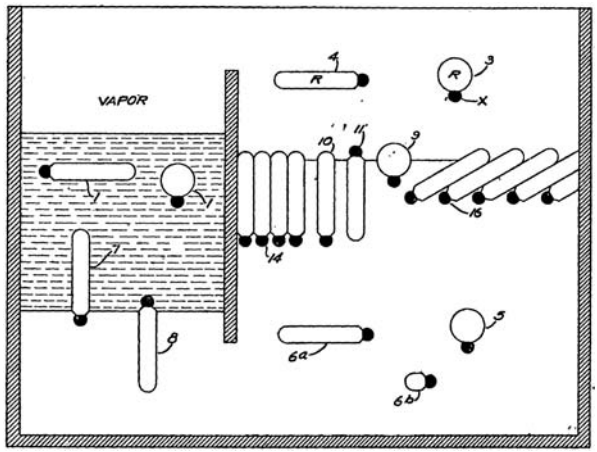

Figure 10.3. Irving Langmuir's diagram explaining "molecular dissymmetry." The small black dots represent a radical active group, and the cylinders represent hydrocarbon chains. From Irving Langmuir, "The Effects of Molecular Dissymmetry on Properties of Matter," in *Colloid Chemistry: Theoretical and Applied*, ed. Jerome Alexander (New York: Chemical Catalog Co., 1926), 525–46, on 538.

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' " (McBain 1926, 9).

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 entitled "An Experimental Test of the Gibbs Adsorption Theorem" (fig. 10.4; McBain and Davies 1927). McBain used a single, four-part "diagrammatic representation" (2231) of a monomolecular film, copying Harkins's diagrams, not Langmuir's. 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 actually seemed to 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" (2230).

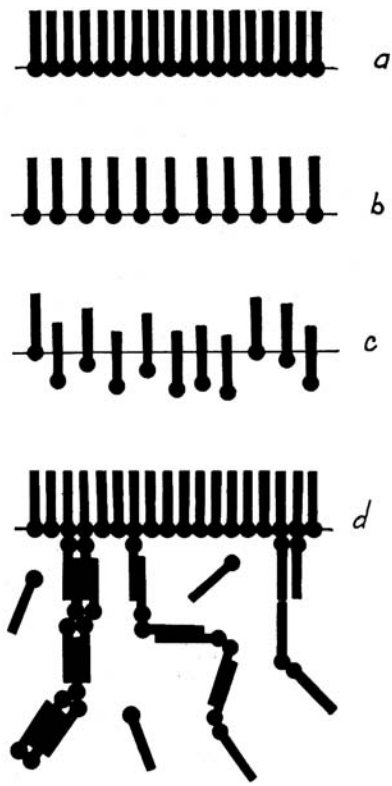

Figure 10.4. Ball-and-stick models of monomolecular films. This may have been the first time the ball-and-stick model was used after Harkins. Reprinted with permission from McBain and Davies 1927, 2231. Copyright 1927 American Chemical Society.

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. 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 the source from which 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's and Langmuir's writing, and given that McBain was a contributor to both of the textbooks for which Harkins had also written. McBain's own work in soap chemistry offers another route of transmission with Harkins: many of Harkins's 1924–25 articles engaged with soap chemistry, and in this context he briefly suggested that the ball-and-stick

model actually represented molecular "wedges" capable of orientation. In 1925, in a popular lecture at 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" (McBain 1925, 581).

This picture of an opposing pair of brushes was accompanied by an overly 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 useful for showing detailed structure but less so for illustrating orientation (fig. 10.5). This connection between Harkins and soap chemistry was also probably not an accident:

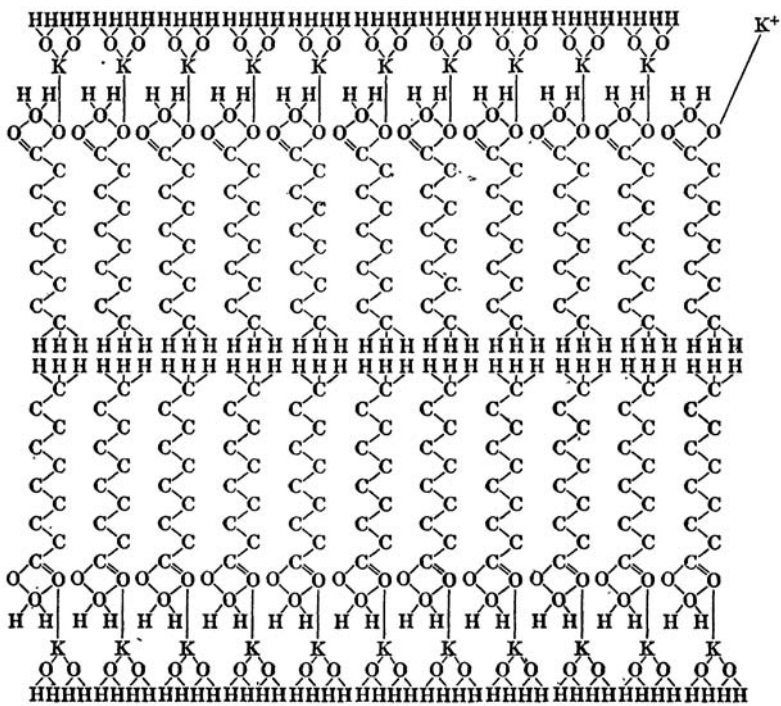

FIGURE 1·1 Diagrammatic cross section of a stable colloidal particle illustrating the principle of "like to like."

Figure 10.5. 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, but was only published later in McBain 1950.

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 (Stadler 2009).

Even more evocatively, McBain also cheerfully suggested that the colloidal particles of soap "resemble a group of, say, less than a dozen eels tied together by the tails, and pointing outwards in all directions from the common centre" (McBain 1925, 582). Although there was some precedent to describing fat molecules as having hydrocarbon "tails" before 1925 (Langmuir 1917, 1864), the verbal convention of referring to lipids as having "heads" as well had become common enough in the 1920s 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. (Lawrence 1929, 132)

This particularly ill-tempered soap chemist was probably the first to publish an illustration of a "sandwich" of fat molecules (fig. 10.6), with tails oriented toward each other, and using the ball-and-stick convention (Stadler 2009, 73–74). This image by A. S. C. Lawrence came from "certain

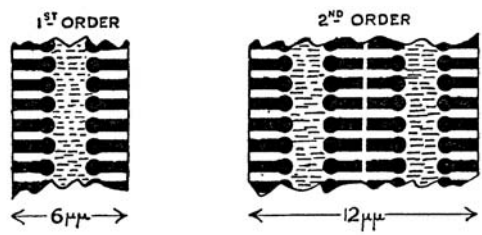

FIG. 59.—Sectional view of black film, diagrammatic.

Figure 10.6. A. S. C. Lawrence's static diagram of very thin soap films, perhaps the first to be shown as a lipid sandwich. This image originally appeared in Lawrence 1929, 128, but it was reproduced and likely more commonly seen in Adam 1930, 137.

a priori possibilities": that is that since a monolayer of fats seems to only exist on a surface of water, two surfaces of water (the shaded regions in fig. 10.6) could support the existence of a bilayer (Lawrence 1929, 11–12). This image was copied and cited in 1930, without mention of the "sandwich" metaphor, 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.

Lipids and the Biological Microworld

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 (Stein 1986). 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 Danielli 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 (Adam 1930, 136–37).

Danielli may have been aware that, in the early 1930s, schematic diagrams of lipids and the structure of fats were slowly spreading across to France and Germany, where the study of fats had become associated with the biology of nerve cells in addition to the physics of soaps. Since 1924, the Giessen biologist Wilhelm J. Schmidt had made a reputation for himself by arguing that animal tissues and cells were made of "building blocks" (*Bausteine*) of submicroscopic, crystalline particles (Schmidt 1924). This was an unusual position for a biologist to take in the 1920s, when most biologists had just recently embraced colloid chemistry as the future for cell research—and in so doing, they had made the decision to avoid microphysical or submicroscopic speculations. The structure of the cell and protoplasm had widely been acknowledged as being a colloid since the late 1890s, giving the view that the cell was a dynamic, heterogeneous aggregate of living slime. For example, through the 1920s, the plant physiologist D. T. MacDougal (1865–1958) was engaged in building artificial plant cells out of gelatin, fats, and filter paper, attempting to create the colloidal structures that mimicked the way plants absorb water (MacDougal 1924). MacDougal's diagram of what he thought was the gradual transition from the colloidal cell wall to the colloidal protoplasm offers an exceptionally

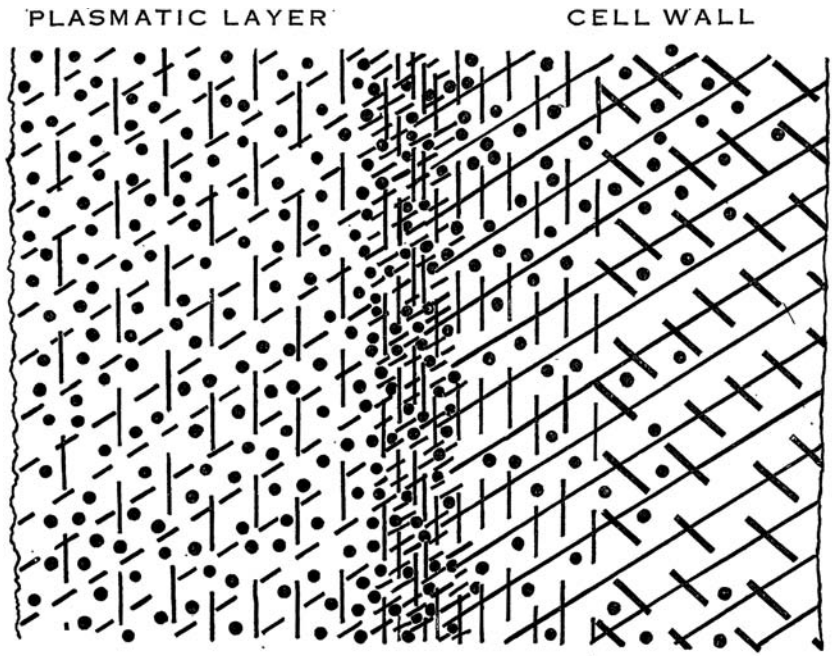

Fig. 1. Diagram of the arrangement of material in the plasmatic layer and cell-wall. / Cellulose. \ Pectin. | Mucilages. / Proteins. ● Fatty substances.

Figure 10.7. D. T. MacDougal's schematic of the colloidal arrangement of the cell wall, lipoidal membrane, and protoplasmic body, showing the three systems as one continuous system, rather than three discrete layers. 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. From MacDougal 1924, 77.

clear (and exceptionally rare) visual insight into how biologists in the 1920s envisioned the cell as a colloidal aggregate: not as a series of clearly delimited anatomical parts, like walls, membranes, or chromosomes, but all as part of a dynamic, polyphase colloidal system, each part blended into the others (fig. 10.7).

Up to 1937, Schmidt was apparently still unaware of Langmuir, Harkins, Adam, and certainly not aware of Danielli and Davson, and none of those names appeared in any of his citations until 1938. Schmidt had been trained as a zoologist in the relatively old-fashioned zoological institute at Bonn in comparative anatomy and natural history. Of those who published in the *Kolloid-Zeitschrift*, Schmidt was perhaps the most naive about physical chemistry, and in none of his writings does Schmidt show more than a

passing acquaintance with topics like surface chemistry or colloidal theory. As a university student, he had taken classes in physics and chemistry, but his interests were in philosophy, art, and classics; and as a graduate student in zoology, he had passions for reptiles, mollusks, and a sunshine-filled life at the various marine research stations along the Mediterranean (Schmidt 1964).

It was around 1910 and probably at the Naples Zoological Station where Schmidt learned polarized light microscopy in order to study oyster shells and mother of pearl, and it was through studying the technique that Schmidt became committed to seeing living cells as being composed of crystalline building blocks rather than unstructured colloidal slime. Polarized light microscopy was a well-known technique to detect anisotropy—directionality or orientation—in crystals and minerals, and it had long been used in mineralogy and geology to identify rocks. Initially, Schmidt began to use polarized light microscopy to study teeth, shells, scales, hair, hard excrescences, and bones. His 1924 comparative anatomy project, *The Building Blocks of Animal Bodies in Polarized Light*, was essentially five hundred pages of detailed examinations of the hard, solid parts of many animals, in the tradition of nineteenth-century comparative anatomy and zoology.

Through the 1920s and into the 1930s, however, Schmidt began to immerse himself in the technical and theoretical approaches to polarized light microscopy that were being promoted by the botanists Hermann Ambronn (1856–1927) and Albert Frey (1900–1988).[10] Ambronn and Frey's ideas promised to give biologists the ability to make reasonable guesses about the submicroscopic structure of the soft, colloidal parts of living cells, such as the unlignified cell wall or the chromatin in chromosomes and nuclei. Their technique relied on a set of optical theories developed by the physicist Otto Wiener (1862–1927), and known as the "Wiener Mischkörper" or "Wiener mixed bodies" (fig. 10.8; Wiener 1904; Wiener 1909). This theory suggested that two idealized colloidal structures would show very specific kinds of birefringence and colorful interference patterns when viewed under cross-polarized light: rodlets arranged in parallel columns within a fluid system would show positive birefringence, while platelets stacked in alternating layers of the same fluid medium would show negative birefringence. Ambronn and Frey (1926) proposed immersing the colloid (or cell or tissue) in a fluid whose refractive index could cancel out the optical properties of the medium surrounding these rods or platelets, thus making any intrinsic optical properties of the rodlets or platelets directly

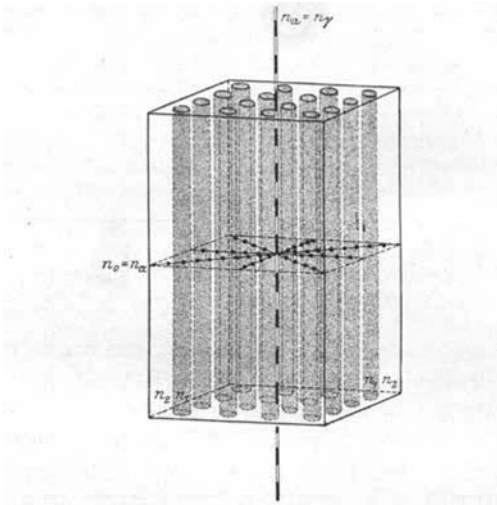

Fig. 25. Zylindermischkörper. $n_a > n_o$, optisch positiv.
n_γ, n_α.

A

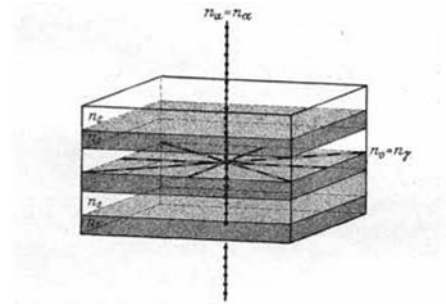

Fig. 26.
Schichtenmischkörper. $n_a < n_o$, optisch negativ.

B

Figure 10.8. Wiener mixed bodies: *A*, rodlet mixed body; *B*, platelet mixed body. If the rodlets and platelets in the two systems were of identical materials, and the media were identical to each other as well, then the rodlet mixed body would always show positive form birefringence parallel to the direction of the rodlets, while the platelet mixed body would always show negative form birefringence perpendicular to the direction of the platelets. From Ambronn and Frey 1926, 114, 119.

accessible. This "imbibition method" would allow the biologist to determine exactly how the submicroscopic rodlets or platelets were arranged within the living tissue, unobscured by the continuous colloidal phase. Ambronn and Frey argued that a good polarization microscopist could separate the "form birefringence" (*Formdoppelbrechung*) of the whole system from the "intrinsic birefringence" (*Eigendoppelbrechung*) of the underlying submicroscopic parts (e.g., parallel rodlets or stacked platelets).

The technique required a great deal of patience, but it had a crucial advantage over traditional cytological fixation and staining: it did not require preserving and killing the cells, which would alter their delicate, submicroscopic, colloidal structure. The first soft tissue Schmidt tackled using Ambronn and Frey's technique was frog eye retina (Schmidt 1935). Schmidt knew that the rod cells especially were delicate complexes of fatty and proteinaceous layers, and at a minimum, he wanted to see if polarization microscopy could allow him to see how they were intertwined. In this 1935

paper, the schematic illustrations are all aimed at working out not only where the fats and proteins are located but whether the proteins and fats showed orientation with respect to one another (fig. 10.9). At this point in 1935, Schmidt believed that living matter was ultimately composed of atoms and molecules, but with the polarized light microscope he could only hint at the directionality of any molecular or supramolecular structures with long dashes.

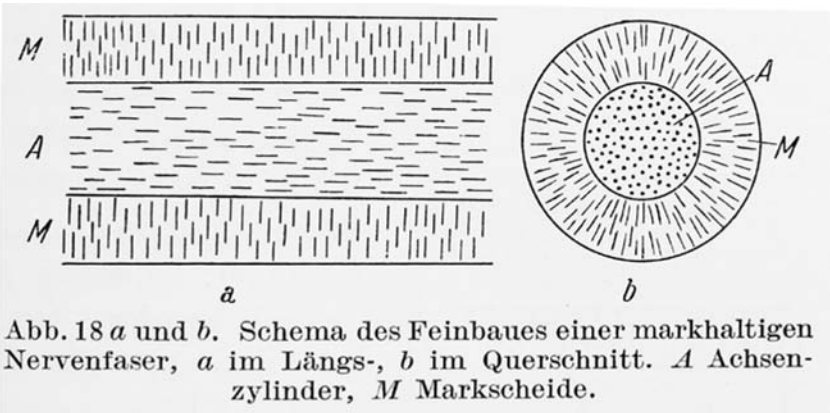

Abb. 18 *a* und *b*. Schema des Feinbaues einer markhaltigen Nervenfaser, *a* im Längs-, *b* im Querschnitt. *A* Achsenzylinder, *M* Markscheide.

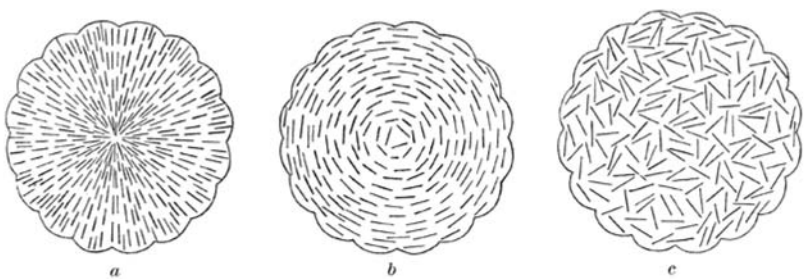

Abb. 21*a*–*c*. Mögliche Anordnungsweisen der Molekeln (bzw. Kolloidteilchen) in der Flächenansicht der nichtlipoiden Schichten des Außengliedes: *a* radiale, *b* tangentiale, *c* regellose Anordnung.

Figure 10.9. Wilhelm J. Schmidt's early attempts to decipher the fine structure of frog eye rod cells. Note that "molecule" and "colloidal particle" are construed as synonyms in the captions, while the images only schematically show oriented particles. The pattern of arrangement of the linear particles in all of these diagrams is meant to guide and predict what kinds of form and intrinsic birefringence might be seen under polarized light. From Schmidt 1935, 513. With permission of Springer.

Between 1935 and 1938, Schmidt began to read more widely on the optical properties and molecular structures of fats and lipids, the same area of physical investigation where surface tension and molecular orientation were built. According to his citation patterns in 1938, Schmidt relied especially heavily on two works by two French scientists. The first was the thin-film chemist Henri Devaux (1931), who had written a comprehensive review article on thin oil films and molecular orientation. Second was the neuroanatomist Jean Nageotte (1936), who had written a monograph on the morphology and polarization optics of lipid gels. Devaux pointed to Langmuir and Harkins's theoretical work, while Nageotte had also incorporated recent French and German X-ray crystallographic research on soap structures. Nageotte was especially attentive to bimolecular lamellar structures, and the only molecular diagram he reproduced was of a bimolecular soap micelle by P. A. Thiessen and R. Spychalski (1931)—each molecule rendered as a very thin ball and stick, arranged in a crystalline rectangle, a fairly distant relative to the icon used by Harkins or McBain. In addition to Nageotte and Devaux, Schmidt was aware of the very influential article in *Protoplasma* by the Dutch colloid chemist H. G. Bungenberg de Jong and J. Bonner (1935), who described birefringent bilayers of lecithin that could self-organize under the right electrostatic conditions. By 1938 Schmidt was beginning to use an iconography of the lipid bilayer structure that would have been very familiar to the surface tension theorists of the 1920s. Schmidt likely came to the ball-and-stick representation through following Nageotte and Devaux's citations—though perhaps he had seen the iconography of molecular orientation at a conference or when chatting with a colleague.

What would have been foreign to workers in the 1920s, however, was Schmidt's complete reliance on a visually inspired language and drawings of shapes of molecules, and his nearly complete abstinence from the complicated physics behind the lipids' shapes and configurations. The phrase "surface tension" ("*Oberflächungspannung*" and variations thereof) appears only three times and only very briefly in Schmidt's first article (1938b) featuring lipid molecules in *Die Naturwissenschaften* (a general audience journal similar to *Science* and *Nature*). When he reprised the article for *Kolloid-Zeitschrift* (1938a) a few months later, he took out any mention of surface tension entirely—an odd move, given the journal. Instead of explanations of fluid or molecular forces, Schmidt provided ten pages of informed guesswork about what kinds of arrangements and materials give rise to specific birefringence patterns, paying close attention to signs of

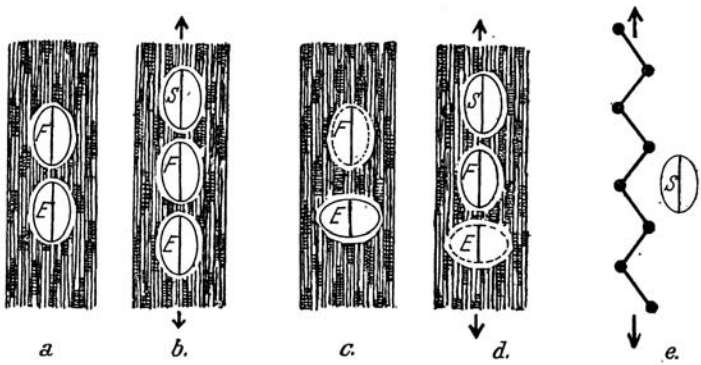

Abb. 48. Spannungsdoppelbrechung (S), erzeugt durch Zug bei einer kollagenen Faser (a, b) mit positiver Form- (F) und Eigendoppelbrechung (E) und bei einer sumachgegerbten kollagenen Faser (c, d) mit positiver Form- und negativer Eigendoppelbrechung; e = Beanspruchung der Valenzbindungen einer Fadenmolekel durch Zug.

Figure 10.10. One of Wilhelm Schmidt's exercises for learning how to interpret structure from polarization optical observation: observing changes in the sign of birefringence as a collagen fiber is pulled. On the left, *a* and *b* are ordinary collagen, showing positive form birefringence and intrinsic birefringence, as well as positive uniaxial strain birefringence. On the right, *c* and *d* are collagen tanned with sumac, showing positive form birefringence and negative intrinsic birefringence, the latter due to the shrinkage caused by the sumac; *e* is a molecular-atomic schematic of the fiber expanding by pulling, resulting in the positive strain birefringence. From Schmidt 1939, 371. With permission of Springer.

physical polarity and directionality he had seen in various kinds of tissues and cells.

This might have been more biology than readers of *Kolloid-Zeitschrift* were used to, but within the discipline Schmidt was fast becoming known as a leading expert on the optical properties of complex colloids. Further, in a long article explaining his techniques to the German Zoological Society in 1939, Schmidt essentially offered any reader a manual to work out how different molecular structures appeared under polarized light. Rather than immediately asking the reader interested in his methods to look at living tissues, Schmidt (1939) offered a few hypothetical diagrams for protein-lipid structures before taking the reader on a series of exercises with chitin, collagen, and lecithin smears. The exercises using exemplary materials were aimed at training the 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 (fig. 10.10). For Schmidt in 1939, molecular structures could be "seen" by

inference and even manipulated on a large scale, regardless of whether the individual molecules were visible or yet rendered on the page.

The last time Schmidt was to write about his methods in depth came in 1941. Soon afterward, World War II left the Giessen zoological institute devoid of all but a few graduate students; the American firebombing campaign on December 6, 1944, leveled most of the city, including Schmidt's library, laboratory, and much of the rest of the university as well (Frey-Wyssling Briefe, 8 May 1946, HS 0443:1059). 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. The realism of these images also represented what he imagined was the fine structure of lipid membranes (fig. 10.11). "*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

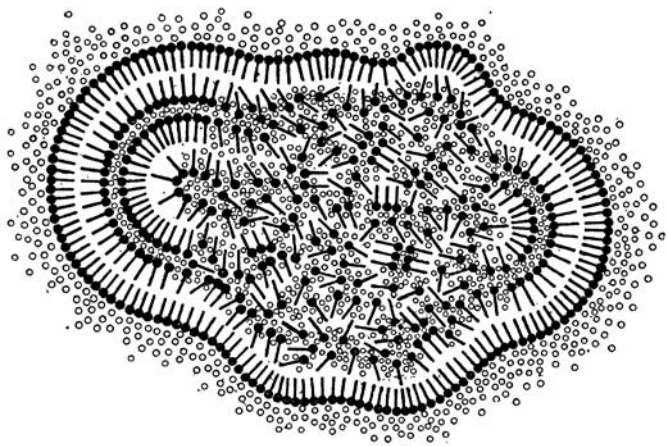

Abb. 6. Lecithinmasse in Wasser (Kreise): Das Wasser ist in das Lecithin eingedrungen; die oberflächlichen Molekeln haben sich mit ihren hydrophilen Polen gegen das umgebende Wasser gekehrt; die so entstandene unimolekulare Lamelle ordnet die anliegenden Molekeln usw.

Figure 10.11. 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." From Schmidt 1941, 44. With permission of Springer.

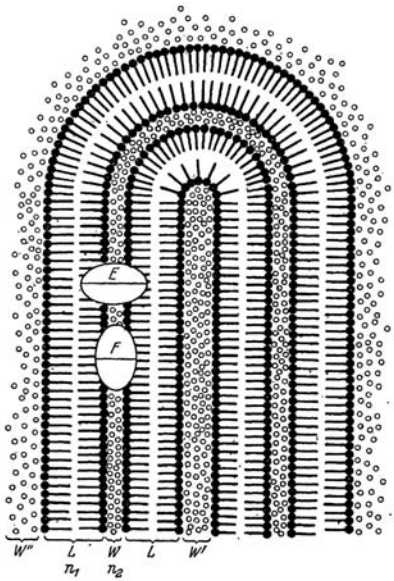

Abb. 7. Feinbau und Optik eines *Myelinschlauches* (oben das freie Ende) am Längsschnitt: *L* bimolekulare Lamelle des Lipoids mit der Brechzahl n_1; *W* Wasserschicht mit der Brechzahl n_2; *W'* axialer Wasserfaden; *W''* umgebendes Wasser. *E* Eigen-, *F* Formdoppelbrechung.

A

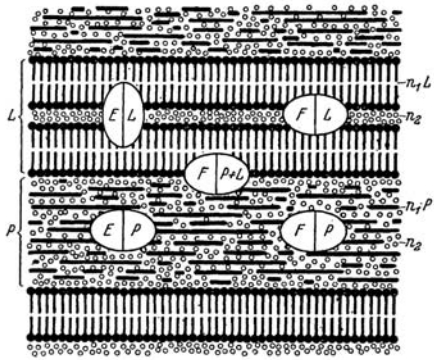

Abb. 8. Feinbau und Optik eines *Schichtsystems* aus *Proteinfolien* (*P*) und *bimolekularen Lipoidlamellen* (*L*) am Durchschnitt. *EP* Eigen-, *FP* Formdoppelbrechung des Proteins; *EL* Eigen-, *FL* Formdoppelbrechung des Lipoids; *F*: *P* + *L* Formdoppelbrechung des Protein-Lipoid-Schichtkörpers; $n_1 P$ Brechzahl des Proteins; $n_1 L$ Brechzahl des Lipoids; n_2 Brechzahl der Zwischenmasse (Wasser).

B

Figure 10.12. Wilhelm Schmidt's diagrams of the myelin figure (*A*) and a layered lipid-protein system in cross-section (*B*). 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. From Schmidt 1941, 45–46. With permission of Springer.

freedom of movement. . . . The ones at the surface 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" (Schmidt 1941, 44).

Not only is the diagram of a mass of lecithin in water especially evocative in its dynamics: the language Schmidt used to animate the lipid molecules was built on reflexive verb constructions to give the molecules agency and individuality. 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 molecular image of the myelin figure and the protein-lipid system that shows how far the iconography of lipids had come as a scientific tool (fig. 10.12). 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 myelin tube would show form birefringence that indicated anisotropy and orientation along the axis of the myelin tube. In fact, Schmidt argued through the image that the intrinsic birefringence of the system—the real arrangement of the individual molecules—is actually perpendicular to the axis of the myelin tube, because of the way lipid molecules orient and arrange themselves into bilayers. 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 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).

Conclusion

The most crucial feature of the two images of lipid systems in figure 10.12 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 between material systems with patterns of darkness 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. In the background were the hard-won, measurable, empirical facts: the birefringence of cells, surface tension measurements, and the lipids' chemical formulas. Transforming these facts into an argument about the cell's molecular structure needed these clear facts, but these alone were not sufficient. Schmidt's images, perhaps even more than his observations, were arguments that the biological microworld really *was* structured in the ways he described and illustrated on paper. Having accepted Schmidt's images as true reflections 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. Schmidt had to be sure that this biological microworld was both real and (inferentially) visible before he could make any scientific claim to the usefulness or veracity of these images. 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. The microworld would be close enough to what he drew on paper, because Schmidt not only imagined that cellular structures looked like this: he assumed cellular structures really *were* this. Arguably, 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 lipids and molecular orientation were obvious to Schmidt 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, Lawrence, or Danielli, I would argue, 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 factual and mathematical rigor of their theories, with images and molecular diagrams useful only in pedagogy or as a heuristic. Schmidt and many biologists and biochemists who followed his example could safely assume that the physics and mathematics were given, embracing the images and other illustrations first and foremost as representations of reality. This departure transformed the idea of the molecule into an entity with both a clear physical identity and, crucially, also 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 10.7 and figures 10.11–12—the former an exceedingly rare illustration seen as having dubious scientific value, and the latter two quite common and seen as essential in 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 used were necessarily second-class citizens: in physical and colloid chemistry, instrumental measurement and mathematical modeling were supposed to provide 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.

Coda: Molecular Imagination and Postwar Technological Progress

Wilhelm Schmidt's evangelism of polarized light microscopy helped inaugurate molecular-scale research of the whole cell, and his writings—and illustrations—from 1935 to 1941 became minor classics in cell research. While he was able, Schmidt established and led a structuralist turn in cell biology, pushing biologists to explore the cell's molecular structure as an alternative to the colloidists' orientation toward physiological function. What Schmidt referred to as the "building blocks" of animal bodies, others variously called this "ultrastructure" research or "submicroscopic morphology," depending on who was asked. By the centenary celebrations of cell theory that began in 1938, submicroscopic morphology was a well-defined specialty in the life sciences, with a significant presence in cytology and technical microscopy journals, two textbooks, and a great deal of energy and excitement (Schmidt 1937; Aschoff, Küster, and Schmidt 1938; Frey-Wyssling 1938). Before the refinement of the electron microscope for biological use, X-ray diffraction was the only method available to examine isolated molecular structures, and polarized light microscopy was the only method available to place molecular structures in the context of the whole cell (Schmitt 1939). Late in life, the American ultrastructural biologist Francis O. Schmitt (1903–1995) could be heard complaining that Watson and Crick had falsely claimed the mantle of "molecular biology" in the 1950s, when, in fact, Schmitt, Schmidt, and others using only polarized light microscopes had been working at the molecular level decades before. "They call all this 'molecular biology,' " Schmitt grumbled. "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 [in the 1930s and 40s]. We were molecular biologists *then*" (1990).

Electron microscopy began to replace polarized light microscopy in ultrastructure research soon after the war, but the transition took well over a decade and varied depending on the kind and style of research (Rasmussen 1997; Strasser 2006). In August 1938, Helmut Ruska (1906–1988) presented one of the first electron micrographs of a cytological object in public, at the Fifth International Congress for Cell Research in Zürich (Ruska 1939; Frey-Wyssling 1964). The existence of this early electron micrograph was more remarkable than the image itself: excitement for the possibility to directly observe the molecular structure of the cell was tempered by concerns about the preparation methods needed to make the technique work. The electron

microscope itself developed faster than biologists' ability to section cells thinly enough to achieve molecular resolutions, and the fixation and metallic staining regimes required to gain contrast were far harsher than the accepted preservation methods in ordinary light microscopy.

Through the 1950s, polarization microscopes were still used to set up expectations for what the electron microscope could see (Schmitt 1960). Even in the best electron micrographs at the time, molecular structures had to be interpreted from the image: for example, the lipid bilayer was visible only by looking for the parallel contrast lines created by the molecular stain of the phosphate group, separated by the measurable length of the two sets of hydrocarbon chains between them. As Rudolf Oldenbourg shows in chapter 12 of this volume, polarized light microscopy itself has become an instrument for precise measurement of molecular dimensions; polarized light microscopy has always had the benefit of not requiring lethal or injurious preparation techniques.

Today the creation and manipulation of images is not only a paper activity for other scientific purposes: model-making is essential, perhaps *the* essential part of structural-molecular theorizing. However, the use of molecular models in biochemistry and molecular biology rarely scales up to the level of whole cells. The epistemological gap between the observation and the molecular-structural theory remained, mediated by the theory and expectations created by the schematic image of molecules in the biologist's mind. Illustrations were widely available across several physical-chemical and biophysical specialties: in the early years of electron microscopy, the theory and illustrations served to confirm the results of the instrument, and not the other way around. The kind of technological progress that made postwar cell biology possible was thus arguably enabled by biologists' expectations and enthusiasms, themselves aided by a healthy molecular imagination.

Acknowledgments

I owe many thanks to Nick Jacobson and Stephen Neal at the University of Wisconsin–Madison's History of Science department, for their edits, ideas, and suggestions in the finishing stages of this essay. Many thanks as well as to Lijing Jiang, Karl Matlin, and Jane Maienschein for inviting me to participate in this collaborative project.

Notes

1 Mathews uses the battery analogy quite indiscriminately to describe any contained, directional sequence of redox reactions, going so far as to argue that "the living cell is in fact a battery" (Cowdry 1924, 68). The "graphite rods" in Mathews' analogy would be carbon

chains whose ends oxidize, providing energy to the cell. This is obviously a biochemical theory, rather than a structural theory based either on observational or physical evidence.

2 Among the significant targets of Jacobs's skepticism was Ernst Overton's famous "lipoid" theory of membrane permeability, which suggested that a lipid-impregnated boundary layer could serve to explain many problems of the protoplast's selective permeability. While Overton's lipoid theory has been repeatedly cited as an origin for modern cell membrane theories, historically Overton was but one of many scientists working on the broader problem of permeability in living cells, artificial membranes, and colloidal precipitates (Lombard 2014, 10–11).

3 Again, by way of example, the seventh section of Mathews's chapter in *General Cytology* is titled "What Is a Molecule?" suggesting that the meaning of "molecule" may have been far from obvious to a novice reader (Cowdry 1924, 38–43). However, Mathews also argues that molecules are held together by gravitation and magnetic moment, and this is just one example of the very strange physics Mathews seems to have embraced—another being a long digression about the four-dimensional luminiferous ether, which "for practical purposes . . . we have called space and time, [and] may be referred to as Infinity and Eternity" (20–25).

4 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.

5 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 (1924a, 153) was so intent on bolstering his priority claim that in a textbook chapter he reproduced a page from one of his student's lecture notes from 1914, which is far from convincing. By 1918 Langmuir (1364) 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's work was neither insubstantial nor unoriginal. Harkins preferred to point out that the British colloid chemist William Bate Hardy had glancingly suggested the idea of molecular orientation in print five years previous (1912, 634).

Patrick Coffey (2008) has shown that several of Harkins's contemporaries thought that Harkins showed a pattern of intellectual theft, although Coffey is intent on highlighting the discord between American scientists in this period. In my judgment, Coffey's claim for Harkins's 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 (McBain and Davies 1927) and Henri Devaux (1931). This may have been either out of ignorance or out of support for Harkins; a few physical chemists, including Neil Kensington Adam (1930) conspicuously avoided citing Harkins and his team, while showering Langmuir with praise.

6 For example Langmuir (1917, 1865) 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 $22\times10^{-16}cm^2$.

7 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.

8 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 to instruments and 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, iodine, bacteriology, physiology, and an extensive rebuttal of Jacques Loeb's recent work on the Donnan equilibrium in protein solutions.

9 This redefinition of colloids was promoted by Wolfgang Ostwald (1907), along with eight classifications for two-phase colloidal systems: gas-liquid (mist), gas-solid (smoke), liquid-gas (foam), liquid-liquid (emulsion, sol, or gel), liquid-solid (suspension, sol, or gel), solid-gas (solid foam), solid-liquid (sol), solid-solid (gel).

10 Albert Frey (later Albert Frey-Wyssling, after he married Margrit Wyssling in 1928) was in many ways Schmidt's counterpart in botany, one of the leaders among biologists pushing for a "submicroscopic morphology" of cells and protoplasm (Schmidt's preferred term was *Feinbau*). Frey, as Schmidt somewhat wistfully remarked, "had the luck of being in the presence of the great masters" of Swiss and German physical chemistry in his education at Zürich and Jena (Schmidt 1964, 224; Häusermann et al. 1960, 7–12).

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