

## “MOLECULAR” VERSUS “COLLOIDAL”: CONTROVERSIES IN BIOLOGY AND BIOCHEMISTRY, 1900–1940\*

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### Introduction

The development of molecular concepts in biology is contrasted mainly with the morphological research of cell biologists and the work of classical geneticists. This has overshadowed a major controversy that, for several decades, shaped the pre-history of what was later called molecular biology: namely the controversy between the molecular and the colloidal conception of the microstructure of cell components. Whereas the molecular conception was based on the notion developed in the 19th century of macromolecules—that is, large molecules with physical and chemical individualities, the competing colloidal theory treated antibodies, enzymes, other proteins and DNA not as macromolecular entities but as colloidal aggregates of a changing composition.

Historians' assessments of the controversy are at variance. According to biochemist-historian Marcel Florkin, the impact of biocolloidy was primarily detrimental because of the pseudoscientific nature of its theories. The search for deeper information on the relations of structure and function was alleviated, according to Florkin, in “irrelevant theories” related to surface actions, electric charges, and adsorption. Thus biocolloidy retarded the development of scientific biochemistry. Florkin called the period in which it strongly influenced biologists' and biochemists' work “the dark age of biocolloidy” (1). Florkin's clear-cut negative assessment has not been shared by other historians. Joseph Fruton, like Florkin

a biochemist and historian, despite highlighting basic flaws of biocolloidy, contradicted Florkin, because in his opinion Florkin dismissed the importance of the physical-chemical approach, in particular the introduction of the concept of adsorption by colloid chemists (2). Surprisingly, however, Fruton also pointed out that the concept of adsorption had been developed long before it was used by colloid chemists (3). Robert Olby considered the emphasis on surface phenomena a positive result of colloid chemistry, though he admits that most of the colloidal work before 1930 has been rejected (4).

Florkin, Fruton, and Olby are in agreement that scientific factors decided the eventual “victory” of the concept of macromolecules over that of colloidal aggregates. In contrast, Pauline Mazumdar emphasizes the role of social factors in determining the outcome of colloidal–molecular controversies that she studied in the history of immunology (5).

What follows is an examination and analysis of major controversies between protagonists of a *colloidal* and a *molecular* biology and biochemistry from 1900 to 1940 (6). They deal with the crucial question, over these four decades, of biological specificity; that is, the specificity of antibodies, enzymes, and what was shown to constitute both, proteins. Controversies in chemistry over the existence and properties of macromolecules largely focused on carbohydrates, though by the late 1920s proteins were included. Notwithstanding the

fact that the controversies took place mostly in separate scientific communities, the influences were mutual. Thus the controversy among chemists over the existence of macromolecules, and in particular its eventual outcome, strongly influenced the controversies in biology.

Here, I highlight the scientific and nonscientific aspects of the controversies, review their roles in determining the outcome, and evaluate their impact on the advance of science and the attitude of scientists. I begin with a short review of the early history of macromolecular and colloidal chemistry insofar as it is related to developments in biology and biochemistry (7).

### Changing Notions of the Constitution of Biologically Active Macromolecules—a Short Overview

#### 1. The idea of polymeric organic molecules in the 19th century and its decline

Kekulé's theories of the four-valent carbon atom and the existence of linear C-C chains (1858) mark the beginning of structural organic chemistry, in which spatial structures were attributed to molecules. During the following decades physiologists and chemists came to believe in the existence of large organic molecules that were held together by what we now call covalent forces. By 1900 chemists had obtained several protein molecules such as hemoglobin in crystalline form. But because of the uncertainty of evidence concerning protein size and structure—there were no appropriate methods to determine their molecular weight and study their structure—and because of seemingly promising alternative hypotheses, the concept of large molecules lost support after 1900 (8). Some protein chemists, however, among them Thomas B. Osborne at Yale, continued work on the preparation of crystalline proteins and their chemical compositions on the assumption that proteins were discrete large molecules.

The rise of physical chemistry and its focus on electrochemical explanations turned attention away from Kekulé's "main valency bond" (later covalent bond), stressing instead the importance of the much weaker physical bonds. The creation of the theory of *Haupt-* and *Nebervalenzen* (primary and secondary valences) in chemical coordination theory by the inorganic chemist Alfred Werner (1902) also encouraged the viewpoint that polymers were not large molecules but rather aggregates of small molecules held together by secondary physical bonds. The first X-ray studies of polymers were

regarded as supporting the view that the so-called high molecular weight substances were in fact aggregates of small crystalline units (micelles, see below).

Emil Fischer, arguably the most eminent organic chemist at the turn of the 20th century, contributed to chemists' neglect and rejection of the concept of macromolecules. He would have accepted the notion of giant organic molecules but did not consider the available evidence for their existence conclusive. Moreover, he did not consider them necessary in order to account for the assumed diversity of proteins, given the large numbers of possible isomers. Fischer's hypothesis that proteins consist of 30 to 40 amino acids, with molecular weights of probably no more than 4000 to 5000 (9) remained prevalent even after his death in 1919. At the same time, the eminent British biochemist Frederick G. Hopkins advised biochemists to deal "not with complex substances which elude ordinary chemical methods, but with simple substances undergoing comprehensible reactions" (10). Following Fischer and Hopkins, most organic chemists focused on the study of small molecules. The study of biologically active "high molecular weight substances" increasingly became the domain of physical chemists and biochemists, who were strongly influenced by colloid chemistry.

#### 2. The development of the chemistry of "colloids"; the rise of "biocolloidy"

The term "colloid" was coined by the British chemist Thomas Graham in 1861 to describe the "pseudosolutions" such as silver chloride or starch described by Francesco Selmi in 1854. Colloids were characterized by a low rate of diffusion through membranes that were permeable to salt solutions, a lack of crystallinity and sedimentation, and a size of at least 1 nm in diameter (in modern terms), and an upper size limit of approximately 1  $\mu\text{m}$ . Until around 1900 colloids remained, as Servos has emphasized, an esoteric topic (11). Then a new interest in colloids arose which led to a flourishing of colloid science in various areas of research until around 1930.

Several reasons may account for the fact that the concept of large molecules lost support after 1900. The advance of novel techniques, for example the availability of new filtration methods and the ultramicroscope, led to a new interest in colloidal phenomena, at first primarily by inorganic chemists. Biologists and biochemists turned to colloidal science because it offered seemingly promising alternative explanations for those basic life phenomena that structural organic chemistry either did not deal with at all or tackled with complicated methods

and uncertain results. For example evidence concerning protein size and structure was ambiguous, relying on difficult methods to determine molecular weight, and without appropriate methods to study their structures (12). Many biologists and biochemists were attracted by the assumption that the phenomena of life followed colloidal laws and could not be explained by structural organic chemistry. Apart from the lack of convincing and convenient alternative practices and the appeal of the new concepts that promised rapid results without the tedious study of the chemistry of substances and processes, the missionary zeal of zoologist-turned-colloidal-scientist Wolfgang Ostwald and his success as discipline builder contributed strongly to the growth of biocolloidy.

Industry was another area where colloid chemistry was in vogue for many years. It was applied in the soap, tobacco, and textile industries. Colloidal chemists empirically succeeded to improve, for example, surface coatings, ceramics, and emulsions. In Germany, at least, the institutionalization of colloid chemistry at universities was in part funded by industry (13).

Among the biologists or physiologists who pioneered the use of colloid chemistry were Carl Nägeli, Franz Hofmeister and, a little later, Wolfgang Ostwald in Germany, and Wilder Bancroft in the United States. A central concept was that of colloidal aggregates, often called micelles, relating to the *Micellartheorie* of Carl Nägeli (14). According to this speculative theory, the “organized substances” in the protoplasm, such as proteins, consisted of crystalline “primary” particles—micelles—that were surrounded by hydration shells. Physiological chemist Franz Hofmeister compared living systems to gelatin that was considered to be a colloid. As colloids, these systems would not possess osmotic properties nor follow the chemical laws of solution.

The main promoter of colloid chemistry in Germany was Wolfgang Ostwald, a son of the physical chemist and Nobel laureate Wilhelm Ostwald (15). His 1915 textbook *Die Welt der vernachlässigten Dimensionen* (The World of Neglected Dimensions) marked a breakthrough for his “biocolloidy.” Ostwald here developed further the theory of the colloidal state of matter, applied to substances that in other respects have nothing in common, such as proteins, gold, soap solutions, solutions of tannic acid, etc. All biochemically relevant substances of the cell such as proteins, enzymes, and nucleic acids were regarded as biologically active colloidal aggregates of undetermined composition. Physiological processes, such as muscle contraction, were explained by increasing or decreasing dispersion of colloids.

In the United States the physical chemist Bancroft became a leading figure in colloid chemistry (16). The physiologist Martin Fischer, an obscure scientist with strong ties to Wolfgang Ostwald, not only strongly propagated colloid-chemical explanations of biological phenomena but also used them in medical treatments in his private practice (17).

During the early 1920s the German organic chemist Hermann Staudinger initiated the concept of macromolecular chemistry. His demonstration of the existence of large molecules held together by covalent bonds, first opposed by almost all of his colleagues, became increasingly accepted after the late 1920s. Biocolloidists were dealt a particularly severe setback when the Swedish colloid chemist Theodor Svedberg, between 1926 and 1930, demonstrated (by means of the ultracentrifuge) the macromolecular nature of hemoglobin and other proteins (and “converted” to macromolecular chemistry). Later findings that many macromolecules include subunits linked by noncovalent bonds did not upset the notion of individual large molecules with well defined physical and chemical structures.

## Controversies

### 1. Controversy over the nature of antibody specificity (around 1900)

The controversy over the nature of antibody specificity started after the publication of Paul Ehrlich’s “side-chain theory of cellular action” (1878) and his further development of the concept of selective affinity, which later became his receptor theory (18). These were inspired by Otto N. Witt’s 1875 theory of color and constitution (19). Ehrlich explained biological specificity, including antibody specificity, entirely in terms of structural chemistry. The idea of a chemical “receptor” gained further prominence through Emil Fischer who, impressed by the stereospecificity of the cleavage of glycosides by enzymes, in 1894 coined the “lock and key” analogy of enzymes and their substrates (20). Ehrlich’s theory implied a sharply defined immunological specificity and a tight binding of the antigen to the antibody. He assumed that lymphocytes possess receptors that combine with antigen and that these receptors are specific because of preformed atom groupings. The theory was rejected by those who preferred explanations based on quantitative differences and denied the existence of sharp specificity in nature. One of them was Max Gruber, professor of hygiene at the University of Vienna, a student of Carl Nägeli, and Max Pettenkofer, both of whom were also

strongly opposed to another concept of sharp specificity, the notion of distinguishable bacterial species, put forward by Ferdinand Cohn and, later, Robert Koch (21).

Colloidal chemists, whose explanations relied on physical concepts such as adsorption and electrical properties, which allowed only for weak specificity, joined Ehrlich's critics. Most outspoken was Wolfgang Pauli in Vienna who turned the controversy into a battle for superiority of colloid chemical over structural chemical explanations of biological specificity. Pauli considered Ehrlich's structural chemistry to be outdated and claimed that there was a colloid-chemical explanation for every single phenomenon in biology and medicine, including immunology. He presented the electrochemical theory of immune affinity developed by Karl Landsteiner as superseding Ehrlich's side-chain theory (22). Landsteiner, a student of Max Gruber, who had received additional training in structural chemistry with Emil Fischer, early on applied colloid chemistry to immunology. He assumed that the affinity between antigen and antibody was due to their electrical charges. For him, however, electrical explanations did not conflict with chemical ones, because he realized the dependence of adsorption on the chemical nature of the adsorbing substance (23).

Collaborators or former students of Ehrlich, such as Heinrich Bechhold and Leonor Michaelis, strongly rejected Pauli's and other colloidists' one-sidedness and their far-reaching claims, criticizing Pauli's disregard of the importance of organic chemistry for biomedical research. Responding to Pauli's reproach that the chemical groups of Ehrlich's side-chains were only fiction, they invoked the authority of Emil Fischer and pointed to the similarity of the "lock and key" and the "receptor" (side-chain) concepts (24).

The controversy ended in an interesting way. The far-reaching claims of the biocolloidists became forgotten after some years. An originally strong supporter of colloid chemical ideas, Landsteiner, by abandoning colloid chemistry, played a crucial role in the further development of immunochemistry in the 1920s. By synthesizing a variety of small organic molecules (haptens) and conjugating them with large carrier molecules to form antigens, which specifically reacted with antibodies, he demonstrated the chemical specificity of the antigen-antibody reaction, thus confirming a central aspect of Ehrlich's assumption (25). But Ehrlich's theory had to be modified later on: the chemical bonds between antigen and antibody were not, as he had thought, "primary valency bonds" (covalent bonds) but consisted of a combination of various weak bonds such as ionic,

hydrogen, hydrophobic, and van der Waals bonds. At first sight, this development might suggest that in the end, molecular and colloidal concepts converged. But a closer view shows that this was not the case. Colloidal chemists did not contribute at all to the examination of the weak bonds that were so important for their aggregate theory. Rather the clarification of the role of these forces in biologically relevant compounds and reactions started from the concepts of molecules and specificity. Theoretical chemist Linus Pauling, who explained the covalent bonds between atoms and molecules in terms of quantum mechanics (26), also contributed greatly to the clarification of the role of weak bonds in macromolecules. Applying X-ray diffraction studies and calculations, he was instrumental in elucidating the role of weak bonds in macromolecules. In 1936 he suggested that hydrogen and other weak forces determine the three-dimensional structure of proteins and were thus a pre-requisite for their function and biological specificity (27). His hypothesis, notably, was based on the notion of proteins as macromolecules (28):

Our conception of a native protein molecule (showing specific properties) is the following: The molecule consists of one polypeptide chain which continues without interruption throughout the molecule (or in certain cases of two or more such chains); this chain is folded into a uniquely defined configuration.

In 1952 he proposed the  $\alpha$ -helix as a structural element in globular proteins, with hydrogen bonds as the most important weak association in the structures of molecules; a year later James Watson and Francis Crick suggested the double helix structure of DNA, with the two chains linked by hydrogen bonds. The paths to the clarification of the important role of weak forces in the compounds and reactions underlying biological specificity successfully bypassed colloid chemistry.

## 2. The nature of enzymes

The history of enzymology is another area of biochemical and biomedical research that was shaped by a number of controversies including, those over molecular and colloidal explanations for enzyme action. After the concept of biocatalysis was first proposed by Berzelius in 1837, a bitter dispute arose between Louis Pasteur, who claimed that alcoholic fermentation was based on whole cells, and chemists, in particular Justus Liebig, according to whom living cells were not required in any fermentation. Liebig believed that ferments (from around 1900 they were called enzymes) were substances in a state of decomposition or combination that acted by transmitting vibration and oxidation (29).

In 1859 Moritz Traube, rejecting Liebig's as well as Pasteur's hypotheses, anticipated the existence of intracellular as well as extracellular enzymes as causes of the most important "vital-chemical" processes in lower and higher organisms (30). But he did not succeed in isolating enzymes from cells. The dispute was finally resolved in 1897 by Eduard Buchner, who demonstrated that alcoholic fermentation also took place in cell-free yeast extracts. Buchner concluded that these extracts contain a fermentation enzyme, zymase, and that fermentation is a chemical process related to specific enzymes. But the controversies between molecular and nonmolecular theories of the mode of action of enzymes were continued.

In the late 19th century leading chemists, among them Bunsen, Buchner, and Fischer, were convinced that enzymes were proteins. Bunsen and Gustav von Hüfner proposed that enzymes were capable of undergoing temporary combinations with fermentable substances (31). Fischer's lock-and-key analogy implied this view. But because of the methodological problems of studying macromolecules and the quickly growing influence of colloid chemistry focused on surface phenomena at colloidal particles of protoplasm as responsible for catalysis, it took 30 years after Buchner's discovery before enzymes were recognized as definite chemical species of the nature of proteins.

Antimolecular and antisubstantialist views remained strong. Nägeli, probably influenced by Liebig, proposed that enzymes act by molecular vibrations communicated to the substrate. His theory (1890) that enzymes were not definite substances but properties of material substances became popular among biocolloidists during the following decades. So did E. Herzfeld's theory (1915), according to which enzymatic actions resulted from certain mixtures of common compounds, e.g. amino acids and peptides (32). Rejecting these antisubstantialist views, Willstätter assumed that small organic molecules, as chemically active groups bound to large nonspecific colloidal material, were responsible for the catalytic process. According to him diluted solutions containing enzymes gave none of the tests for proteins, and he concluded as late as 1926 that enzymes were not of a protein-like nature (33).

A member of Emil Abderhalden's school in Halle, Andor Fodor in the 1920s proposed a colloid chemical theory, according to which cellular colloids such as proteins, lipids, and polysaccharides build a gelatin system in the protoplasm on whose numerous interfaces enzymatically active substances or groups operate (34).

The controversy on the nature of enzymes ended with the publication of new experimental evidence in favor of the old theory that enzymes were distinct proteins: In 1926 the American physiologist James B. Sumner, through purification and crystallization of the enzyme urease from jack beans, showed that this enzyme was a pure protein (35). Opponents to this view, in particular Willstätter and members of his school, at first tried to dismiss the achievement as being the crystallization only of a protein "carrier" of the real enzyme. But when John Northrop and Moritz Kunitz purified and crystallized several digestive enzymes as discrete proteins with the active center being part of the protein molecule, the view that enzymes were proteins gradually became generally accepted (36).

The end of the controversies over the nature of enzyme action was thus marked by an experiment that may be called crucial even though its implications were not immediately accepted by all workers in the field. This experiment and those that confirmed its results shortly thereafter became the starting point for research on the mechanism of enzyme action.

### 3. Controversy over the molecular nature of proteins

The recognition of enzymes as proteins coincided with the recognition of proteins as molecules. After 1900 biocolloidists considered proteins, which became a focus of their research, to be aggregates of small molecules (37). Despite the fact that many protein chemists, in particular in the United States, continued to crystallize proteins and were convinced of high molecular weights of proteins (38), protein chemistry, too, was affected by colloid chemistry (see section 4 below). One of the strongest supporters of colloid chemical concepts in protein and enzyme research was Emil Abderhalden in Germany (39). Biocolloidists claimed that the physicochemical laws of solution were inapplicable to proteins and that they did not form salts in chemical reactions but adsorbed substances such as dyes and hydrogen ions at their surfaces.

A different view was taken by those protein chemists and physical chemists, who at the beginning of the 20th century examined the importance of the ionic environment, a core concept of early physical chemistry, in protein chemistry. Mainly due to the work of Soeren Soerensen and Leonor Michaelis, the concept of the hydrogen ion concentration became the foundation of an exact physical chemistry of proteins, including enzymes. Subsequently Loeb played a crucial role in criticizing colloidal theories concerning proteins, show-

ing that they were obsolete. Loeb was a physiologist who, rejecting vitalistic and metaphysical explanations, became a pioneer in the search for physical and chemical explanations of biological phenomena. Like some other critics of colloid chemistry, such as Landsteiner and Michaelis, Loeb at first considered the colloidal approach potentially useful though he was not happy about its vague explanations. But his opposition to biocolloidists' far-reaching claims, which he rejected for scientific, philosophical, and political reasons, grew rapidly when colloidal chemistry gained influence. The scientist who strongly contributed to rendering these claims popular in the United States was Wolfgang Ostwald, whom Loeb knew well. Because of his good relationship with Ostwald's father, Wilhelm, Loeb invited Wolfgang to spend two postdoctoral years (1904-6) at his laboratory in Berkeley. Ostwald, however, disdained hypothesis-driven experimentation such as Loeb's "schlagende Versuche," preferring instead descriptive research such as "schematical series of experiments" (40). Much to the dislike of Loeb, he began to explain physiological phenomena entirely in terms of colloid chemistry, that is by coagulation and degrees of dispersion of cell components. His neglect of experiment and tendency towards speculation generated a conflict with Loeb; Ostwald's stipend was not extended (41).

During 1913-14 Ostwald was invited to give an extended lecture tour in the United States, where he was warmly received (42). He attempted to convince his audiences of the importance and fundamental new character of colloid chemistry, arguing that colloids constituted the most universal and common of all things we know; they formed a world of neglected dimensions, a middle country between the chemical and microscopic levels, following special yet undiscovered colloid-chemical laws. Therefore colloid chemistry deserved the right "to existence as a separate and independent science" (43). Five of these lectures were included in Ostwald's popular *The World of Neglected Dimensions* (44). Arguments such as that physical chemistry could not account for membrane phenomena since biological systems could not be described in mechanistic terms, were explicitly directed against Loeb's basic convictions. Despite initial enthusiasm for Ostwald's colloid chemistry in the United States, there were critical voices, among them the physiologist Albert P. Mathews who condemned the confusion of descriptive and explanatory terms (45). The most fundamental attack came, however, from Loeb.

According to Loeb's biographer Philip Pauly, Ostwald's views formed for Loeb "a particularly pernicious

basis for 'metaphysical romance.'" Moreover, Ostwald exemplified the links Loeb saw between romantic attitudes in science and militaristic nationalism. The assertion that a "'neglected middle country' of colloids had 'a right to exist' paralleled German claims for the defense of 'middle Europe'" (46). The preface, written "from the trenches" in France, supported this view (47). Similarly, Loeb resented Wilhelm Ostwald's rabid nationalism during the war, which aimed at the unification of Europe under German supremacy, and their friendship turned cool (48). Loeb's aversion to the vague, speculative, and inherently vitalistic concepts of colloid chemists and his concern about their increasing acceptance by American scientists such as Bancroft prompted him to refute these claims by experiment. When in 1917 a coworker of Arrhenius and Soerensen brought a new electrical pH meter to the Rockefeller Institute, of which Loeb was by then a member, Loeb gave up all his other projects and produced a long series of publications on proteins and membrane equilibria, culminating in his 1922 *Proteins and the Theory of Colloidal Behavior* (49). Here he showed, first, that the colloidist concept of aggregation was superfluous because proteins obeyed the stoichiometric laws of chemical combination. Second, he made it clear that the physical properties of colloidal proteins, such as osmotic pressure and electrical potential, could be derived from existing theories of physical chemistry, such as the Donnan equilibrium and the theory of solution, if the influence of different pH values was taken into account. In principle, Loeb saw the chemistry of proteins as no different from that of small molecules. He concluded a paper in German in *Die Naturwissenschaften* the following year with the statement (50):

It is possible to explain quantitatively the colloidal behavior of proteins on the basis of theoretical mathematical derivations. The so-called colloid chemistry that initially gave the impression of a new chemistry appears to have been based only on the non-observance of a condition of equilibrium of classical chemistry, at least insofar as proteins are concerned.

The editor of *Die Naturwissenschaften*, Arnold Berliner, was strongly criticized by German colloid chemists for publishing this article (51). The *Kolloid-Zeitschrift* published several counterstatements, including one by its editor Wolfgang Ostwald, who rejected Loeb's "purely chemical theory" for the behavior of proteins as a mere "fallacy". Though outside Germany Loeb's view became increasingly accepted (52), the controversy over proteins was not resolved because Loeb could not present conclusive evidence for their molecular weights or specify their structures. Only when Svedberg, using an ultracentrifuge,

demonstrated the macromolecular nature of proteins in sedimentation studies at the end of the 1920s, did the concept become generally accepted.

Shortly thereafter, the molecular nature of proteins was used with great success in applied research. As Creager has shown, the “molecularizing” of protein chemistry brought about one of the most celebrated advances in military medicine during WWII, namely the development of blood plasma fractions as therapeutic agents (53). The scientist responsible for this success was Edwin Cohn, head of the Department of Physical Chemistry at Harvard Medical School, who together with Edsall during the 1930s systematically studied proteins as macromolecular polyelectrolytes (54). According to Creager (53):

...the transition in military medicine from reliance on colloidal chemistry [in WWI] to physical chemistry of solutions (as assimilated into biochemistry) [in WWII] reveals the process of molecularization which had occurred within biomedical research in the intervening decades.

Cohn’s and Edsall’s textbook on proteins (1943) became the standard work for protein biochemists during the next decades (55).

#### 4. The controversies over the existence and properties of macromolecules in chemistry

With a focus mostly on cellulose and other chain molecules comprised of small repeating units such as caoutchouc, the controversy over macromolecules in chemistry in the 1920s took a different course from that over antibodies, enzymes, and proteins. Chain molecules do not possess a uniform molecular weight and have a much less specific structure than globular proteins. Thus the controversies were not about specificity but about the existence of large molecules, the range of chain lengths, and physical properties of the molecules. As with the other controversies, the disputes were shaped by the personalities of those involved. Following is a summary of the main levels of the controversies (56).

The controversy over the existence of macromolecules was initiated by Staudinger, who in 1920 stated—still without experimental evidence—that various artificial products of polymerization, for example polymeric ketenes, “can be explained sufficiently by normal valency formula” (that is they are linked by covalent bonds), thus contradicting the widespread opinion that these products were compounds linked by secondary valencies (weak bonds) (57). The article was generally neglected. A year later, Freudenberg, as a result of his

analysis of cellulose degradation studies, published the hypothesis that cellulose consisted of ca. 100 equally bound glucose units, the first evidence for the existence of long chain molecules in cellulose (58).

A few years later Staudinger provided experimental evidence for his theory and introduced the term “Makromolekül” for giant molecules whose subunits were linked by covalent bonds (59). Chemists from various subdisciplines opposed his theory (60). It did not help that he was already a much respected member of the community of organic chemists, with contributions on ketenes and organic phosphorus compounds. Responding to methodological criticism, he began to investigate simple synthetic products whose monomeric components were well known, using them as models for polymeric substances and transferring his experimental results by way of analogy to natural products such as caoutchouc and cellulose.

Most of Staudinger’s colleagues at the ETH in Zürich, where he was a professor until his call to Freiburg in 1926, rejected the macromolecular theory. At a meeting of the Zürich Chemical Society in 1924, the mineralogist Paul Niggli, the organic chemist and future Nobel laureate Paul Karrer, and the physicist Paul Scherrer were among his many opponents. Different methodologies played an important role, the main objections coming from X-ray crystallographers such as Scherrer who considered Staudinger’s claim a contradiction of their own interpretations.

Likewise, Staudinger was attacked, in particular by organic chemists, at the 1926 Düsseldorf meeting of the Society of German Scientists and Physicians, which was chaired by Willstätter. Fritz Haber was actively involved in choosing participants. According to Yasu Furukawa, Haber chose advocates of the aggregate theory, such as Max Bergmann, Hans Pringsheim, and Hermann (later Herman) Mark to take a stand against Staudinger and his macromolecular view (61). Since Haber did not conduct research in this field himself, he might have been motivated by the fact that members of his institute (in particular Herbert Freundlich) and colleagues from other KWIs (such as Bergmann, Reginald Herzog and Kurt Hess) then supported the aggregate theory. Moreover, one cannot exclude the possibility that he may have wished to see Staudinger publicly criticized, given the fact that their erstwhile friendship came to an end when Staudinger attacked the use of poison gas during WWI.

Several hundred chemists listened to Bergmann, Pringsheim, and Ernst Waldschmidt-Leitz present ar-

guments for the aggregate theory of polysaccharides and proteins. Staudinger, with his paper "Die Chemie der hochmolekularen organischen Stoffe im Sinne der Kekulé'schen Strukturlehre," alone defended the macromolecular view. Somewhat surprisingly, however, the position of Mark, who had supported the aggregate theory earlier, was almost neutral; according to him small unit cells in the X-ray pictures did not preclude the existence of large molecules. Moreover, after a long and fierce discussion of Staudinger's contribution, Willstätter, who chaired the session, became convinced of the possibility that large molecules of a molecular weight of 100,000 existed, despite the fact that this was still a "terrifying concept" to him (62).

During the next couple of years some scientists changed their opinions and started to conduct research based on the concept of macromolecules. Among them were Bergmann, Mark, and Kurt H. Meyer. Bergmann in 1932 succeeded (with Leonidas Zervas) to develop a method to synthesize large specific peptides (carbobenzyloxy method), thus opening up a new era in the growing field of peptide synthesis. Mark and Meyer became leading polymer researchers in Germany, focusing on physical chemical methods, in particular X-ray diffraction.

The macromolecular concept received a crucial confirmation through Svedberg's demonstration of the macromolecular nature of proteins. By 1930 most organic chemists were no longer opposed to the idea of macromolecules, even though they were not interested in undertaking research on them. It was the X-ray crystallographers who began to examine the structure of organic macromolecules. The controversy with Staudinger was, however, not ended. On the one hand, it was continued with colloid chemists, in particular Wolfgang Ostwald and Kurt Hess, who remained opposed to the concept (63). On the other, Staudinger opened up, surprisingly, an even fiercer controversy with his erstwhile opponents Mark and Meyer despite the fact that they were among the first to support his theory. Meyer and Mark in 1928 accepted Staudinger's view in principle but modified it. Confirming through X-ray crystallography Freudenberg's hypothesis, according to which cellulose consists of long chains of glucose molecules (they assumed 30 to 50) linked by glycoside bonds, they suggested using the term *Hauptvalenzkette* (main valency chain) instead of macromolecule preferred by Staudinger, because the term molecule connoted discrete compounds of a specific size that were not linked with each other (64). The glucose chains in cellulose were, however, of various lengths and linked to each other by weak forces (van der Waals

forces). Questioning Staudinger's life-long assumption that macromolecules were rigid and did not bend, Meyer explained the elasticity of caoutchouc by the tendency of its isoprene compounds to bend and twist (65). Whereas later research proved Mark and Meyer correct in their assumption of intermolecular forces and molecular flexibility, it showed that cellulose molecules were much larger than they had assumed.

The new controversy centered around several issues: terminology (Staudinger's *Makromolekül* prevailed over *Hauptvalenzkette*, but Mark's later suggestion of *polymer* became widely accepted); methodology (Staudinger remained skeptical of physical chemical methods); contradictory interpretations of experimental results; dogma (the rigid molecule); and, perhaps most important for the fierceness of Staudinger's attacks, priority. The arguments were played out between 1928 and 1936 in the *Berichte der deutschen chemischen Gesellschaft*. The dispute was continued after 1932 when Mark moved to Vienna and Meyer to Geneva. Only in 1936 did the editorial board officially bring it to a close, following the 140th communication by Staudinger on macromolecules, an uncompromising attack on Meyer (66).

What followed was what might be called a bad play. Staudinger who at the same time had a fierce dispute with Kurt Hess, whom he reproached for having distorted his (Staudinger's) statements, tried to persuade industry to intervene (both men were beneficiaries of IG Farben funding). Among other things Staudinger presented himself as a victim of the Jews, that is of Mark and Meyer (Mark's father was Jewish). But his sponsor from IG Farben, Georg Kränzlein, a member of the NSDAP and SS, considered Staudinger's ongoing controversies with erstwhile opponents as senseless and counterproductive, and advised him to stop "quarreling with Jews" and "ignore them," in accord with the Nuremberg Laws (67). Moreover, Staudinger's good relationship with IG Farben suffered when he criticized the firm for having allowed Meyer to attack his (Staudinger's) viewpoint in the 1920s when Meyer was a member of the firm's board (68).

This short account shows that various factors contributed to the generation and conduct of the controversies over the existence and properties of macromolecules, among them dogma (organic chemists' "large molecules do not exist," and Staudinger's "macromolecules do not bend"), conflicting interpretations over the use of different methods, change of attitudes, and personal features. The controversy in the 1920s was largely one with Staudinger. He stood his ground with grim determination despite the fact that he was attacked fiercely

from all sides and had few allies (he even seemed to prefer to fight alone, and did not try to join forces with Freudenberg). His stubbornness and dogmatic way of arguing prolonged, however, the controversy at a time when his view had long been accepted, preventing him from conducting more productive research later on.

### Summary and Conclusion

The historically interesting questions dealt with in this paper concern: (1) the impact of the controversies dealt with on scientific advancement; (2) their influence on scientists' opinions and practices; and (3) the role played by social and scientific factors. What follow are a summary and comment on the conclusions drawn in the four case studies.

#### (1) Impact of the controversies on scientific advancement

This study largely supports the view of Marcel Florin that the controversies over the claims of biocolloidists had primarily a retarding impact on the development of biology and biochemistry. At a time when clear cut evidence for large specific molecules was not yet available, these claims discouraged further research on the molecular structure of enzymes, other proteins, and DNA and its relationship to function, that is, research that eventually provided explanations for biological specificity. Chemists focused their work on the structures of small subunits, that is, peptides and nucleotides. To give an example from DNA research: The Swedish cytochemist, Einar Hammarsten was one of the few researchers who dealt with polymeric, nondegraded DNA. But at that time he did not consider it necessary to examine its properties. Instead he explained the biological action of DNA through its ability to act on small environmental changes as a colloid, that is, to increase or reduce its state of aggregation and thus influence the physico-chemical properties, such as osmotic pressure, of the nucleoplasm (69). (Nevertheless, in 1938 he was one of the researchers who established the macromolecular nature of DNA.)

Despite the fact that some laboratory technologies developed by colloid chemists, most importantly the ultracentrifuge, proved highly fertile, the conduct of colloidal chemical research in the area of biology and biochemistry did not lead to any major scientific success. Even the nature of the weak forces, a key element of colloid chemistry, and their role in biologically relevant substances such as proteins, were elucidated by chemists on

the basis of the macromolecular concept. The influence of biocolloidy and the often associated focus on applied research in medical biochemistry, at least in Germany, was detrimental to the development of biochemistry by marginalizing excellent biomedical scientists who had abandoned colloid chemistry. According to Michaelis, it was impossible for a biochemist in Germany to receive an academic position, if one did not aim at "so called 'practical' successes" (70). In Europe it appeared to be advantageous to pursue a colloidal chemical approach in order to receive an academic position in biochemistry (71). Lipmann was another leading biochemist active in the 1920s and 1930s who shared Florin's view of a negative impact of colloid chemistry on the development of an exact scientific biochemistry (72):

It seemed sufficient to call [the protoplasm] colloid in order to give the impression to understand something about it.

According to Fruton, the most significant feature of the debate about proteins and enzymes between 1900 and 1930 was the tension between biologists and biochemists, using the physical chemical approach of the colloid chemists, and organic chemists and biochemists following the tradition of Emil Fischer (73). These tensions were indeed a main feature of the controversy about Ehrlich's side-chain theory. But with organic chemists hardly participating in the controversies in protein chemistry and biochemistry later on, the main controversies here took place between colloidal chemists on the one side and a few physical chemists and biochemists on the other, all using physico-chemical methods. By applying the ionists' concept of physical chemistry and following the tradition of Fischer (and also of Ehrlich), certain researchers fought the prevailing claims of colloidal chemists engaged in biological and biochemical research, most notably Loeb, Cohn, and Edsall.

#### (2) Influence of the controversies on scientists' opinions and practices

It is not possible to assess the amount of learning brought about by the arguments exchanged in the controversies analyzed above. As in other controversies, many scientists remained intransigent; others changed their attitudes either quietly or explicitly. In some cases, scientists' readiness to change their opinions and practices proved crucial for their own success and for further scientific developments. Among them are the following:

- Karl Landsteiner, an active early supporter of colloid chemistry, later changed his approach, accepting the existence of sharp specificity and

including organic chemistry as a tool in his most fruitful studies on the chemistry of antigenic specificity.

- Hermann Mark, in the controversy about the existence of macromolecules, changed his research program and subsequently conducted physical chemical studies on macromolecules (or polymers, as he preferred to call them) that proved of high theoretical and practical value.
- Otto Warburg conducted his most outstanding and internationally pioneering research on enzymes only after he had changed his research program and based it on the notion of enzymes being proteins, following evidence provided by Sumner and Northrop in the late 1920s. In the 1930s Warburg isolated and characterized chemically and physically a number of enzymes active in the oxidative degradation of glucose in the cell, that is glycolysis and the respiratory chain.

### (3) The role of scientific and social factors

The cases presented here show that social and political factors influenced the course and duration of the disputes. But they also show that the controversies over the existence of macromolecules and the molecular or colloidal nature of major biologically relevant substances and reactions ended by the late 1920s because there was new, convincing scientific evidence in favor of the macromolecular theory, which soon became generally accepted. Most historians agree that scientific factors played a major role in closing the disputes, but they disagree about the importance of social factors, some, like Mazumdar, attributing a determining influence to them. She here followed the “Denkstil” concept of Ludwik Fleck, pointing to the fact that probably this concept itself had grown out of the colloidal-molecular controversy in immunology. Fleck in 1935 rejected the treatment of toxins and receptors as chemical entities, calling Ehrlich’s “Denkstil” “a primitive scheme,” which “is being progressively discarded in accordance with current physico-chemical and colloidal theories” (74). Fleck’s awareness of the differences between the “Denkstile” prevalent in various schools—that is the concept of absolute specificity in the Ehrlich school and his own “Denkstil” based on colloid and the rejection of sharp specificities—according to Mazumdar, induced him to set up the claim of the socially conditioned nature of scientific facts. Following Fleck, Mazumdar concludes that ideas must be fitted into a social power structure in order to acquire authority.

I argue that this assumption cannot explain major features of the colloidal – macromolecular controversy and their closure. It is true; there was no scientifically “logical” path to the general acceptance of the macromolecular concept. Social and psychological factors, for example the influence of schools, the seductive property of colloidal concepts described by Florin, the organizational skills and initial high reputation of Wolfgang Ostwald (related to the renown of his father), and the support provided by industry played important roles in the rise of colloidal chemistry. But social factors cannot explain the rise of macromolecular chemistry and biology and the end of colloidal chemistry (as far as biology and biochemistry are concerned). In general, social factors do not explain the fact that new concepts or theories, developed by people without power or prominence, sometimes replace predominant concepts and theories. Macromolecular chemistry, initiated and promoted by the organic chemist Hermann Staudinger, who in doing so became an outsider of his discipline, is a case in point.

In order to explain the outcome of the controversies and the fact that it was molecular biology which has been advancing rapidly during the past half century and not colloidal biology, we need to compare the scientific quality of these two approaches. By applying the criteria of epistemological reliabilism (75) *molecular* biology can be shown to be superior to *colloidal* biology, because

- the existence of macromolecules and the macromolecular nature of biologically active molecules like proteins or DNA have been abundantly confirmed by *reliable* experiments, conducted with the help of a vast range of different methods;
- the macromolecular approach has been *relevant* for answering pertinent questions in biology such as that of the nature of the genetic material, its replication and mutation, because it could be combined with the fruitful concepts of the gene and the chromosome theory, whereas the colloidal approach with its concepts of “ideoplasm” (Nägeli) and adsorption of hereditary enzymes to chromatin (R. Goldschmidt), had already lost its relevance during the development of classical genetics.
- the macromolecular concept has become *fruitful* in further empirical and theoretical biological, biochemical, and genetic research where it has led to major scientific advances. It has become

a basic unit in biological, pharmaceutical, and medical applications as the increasing importance of “molecular medicine” indicates.

It is true, to quote Linus Pauling, that there are “many aspects of life that are not yet accounted for in a detailed way on a molecular basis” (76). Yet, it is also true, as Pauling continued, that within a relatively short period of molecularization in biology—he spoke of thirty years culminating in the elucidation of the DNA double helix structure by Watson and Crick—“a thoroughly satisfying understanding of many of the properties of living organisms in terms of the structure of the molecules of which they are composed” had been achieved.

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### REFERENCES AND NOTES

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1. M. Florin, *A History of Biochemistry*, Elsevier, Amsterdam, London, 1972, 279-280. “Its supporters claimed that many biological phenomena such as parthenogenesis, muscle contraction, production of action currents in nerves, heart activity, ciliary movements, etc. were influenced by inorganic ions according to a series of degrees of influence of the same series of ions on heat coagulation, on lecithin precipitation, etc. The induction that biological phenomena were the results of changes introduced by ions in agglutination, lytic processes, dispersion, hydration, or dehydration of colloid micelles believed to compose the protoplasmic ‘gel’ became widespread.”
2. J. S. Fruton, *Proteins, Enzymes, Genes. The Interplay of Chemistry and Biology*, Yale University Press, New Haven, CT and London, 1999, 158.
3. Ref. 2, *Proteins*, pp 203-204; see also J. S. Fruton, *Molecules and Life. Historical Essays on the Interplay of Chemistry and Biology*, Wiley-Interscience, New York, London, 1972, 140-1.
4. R. Olby, “Structural and Dynamical Explanations in the World of Neglected Dimensions,” in T. J. Horder, J. A. Witkowski, and C. C. Wylie, *A History of Embryology*, Cambridge University Press, Cambridge, 1985.
5. P. Mazumdar, *Species and Specificity*, Cambridge University Press, Cambridge, 1995.
6. Since “molecular” in this context relates to macromolecules, for reasons of simplicity, I will use in the following, the term molecule instead of macromolecule. Angela Creager has used the term molecule in the same way in “Producing Molecular Therapeutics from Human Blood. Edwin Cohn’s Wartime Enterprise”, in S. de Chadarevian and H. Kamminga, Ed., *Molecularizing Biology and Medicine. New Practices and Alliances, 1910s–1970s*, Overseas Publishers Association, Amsterdam, 1998, 107-138.
7. For a comprehensive history, see, for example a) H. and M. Staudinger, *Die makromolekulare Chemie und ihre Bedeutung für die Protoplasmaforschung*, Springer, Wien, 1954; b) H. Staudinger, *Arbeits Erinnerungen*, Dr. Alfred Hüthig, Heidelberg, 1961; c) J. T. Edsall, “Proteins as Macromolecules: An Essay on the Development of the Macromolecule Concept and some of its Vicissitudes,” *Arch. Biochem. Biophys.*, **1962**, Suppl. 1, 12-20; d) C. Priesner, H. Staudinger, H. Mark, K. H. Meyer. *Thesen zur Größe und Struktur der Makromoleküle*, Verlag Chemie, Weinheim, 1980; e) Y. Furukawa, *Inventing Polymer Science. Staudinger, Carothers, and the Emergence of Macromolecular Chemistry*, University of Pennsylvania Press, Philadelphia, PA, 1998 f) Y. Furukawa, “Macromolecules. Their Structures and Functions,” in M. J. Nye, Ed., *The Modern Physical and Mathematical Sciences*, Cambridge Univ. Press, Cambridge, MA, 2003, 429-445; Ref. 3.
8. J. T. Edsall, “Physical Chemistry of Proteins 1898-1940,” in P. R. Srinivasan et al., “The Origin of Modern Biochemistry: a Retrospect on Proteins,” *Ann. N. Y. Acad. Sci.*, **1979**, 325, 53-73 (54-57).
9. See for example E. Fischer, “Isomerie der Polypeptide,” *Z. Physiol. Chem.*, **1917**, 99, 54-66.
10. Ref. 2, pp 159-160.
11. J. W. Servos, *Physical Chemistry from Ostwald to Pauling. The Making of a Science in America*, Princeton University Press, Princeton, NJ, 1990, 300.
12. As far as scientists’ motives are concerned, we also may, following Pauline Mazumdar (Ref. 5), invoke a predilection for research styles. The fact that colloidal science emphasized graded differences and smooth transitions may have appealed to scientists with a predilection for this type of explanation over that in which specificity and diversity in nature were prevalent (see Ref. 25). But motives cannot explain the long-term continuation of practices.
13. U. Deichmann, *Flüchten, Mitmachen, Vergessen. Chemiker und Biochemiker in der NS-Zeit*, Wiley/VCH, Weinheim, 2001, Ch. 7.2.
14. Ref. 7a, p 10.
15. Ref. 13.
16. J. W. Servos, “A Disciplinary Program that Failed: Wilder D. Bancroft and the *J. Phys. Chem.*, 1896-1933”, *Isis*, **1982**, 73, 207-232.
17. Ref. 13, Ch. 7, part 2.
18. Mazumdar has dealt in detail with the controversies in immunology (Ref. 5).

19. A. S. Travis, "Science as Receptor of Technology. Paul Ehrlich and the Synthetic Dyestuffs Industry," *Science in Context*, **1989**, 3, 383-408.
20. E. Fischer, "Einfluß der Konfiguration auf die Wirkung der Enzyme, I." *Ber. Dtsch. Chem. Ges.*, **1894**, 27, 2985-2993.
21. U. Deichmann, "Empiricism and the Discreteness of Nature: Ferdinand Cohn (1828-1998), the Founder of Microbiology," in U. Charpa and U. Deichmann, *Jews and Sciences in German Contexts. Case Studies from the 19th and 20th Centuries*, Mohr-Siebeck, Tübingen, 2007, 39-50.
22. "Festival lecture" to the K.K. Gesellschaft der Ärzte in Wien of 1905, cited in Ref. 5, p 227.
23. Ref. 5, p 231.
24. Ref. 5, pp 220-236.
25. According to Mazumdar, Landsteiner preferred the "unitarian" thought style of graded differences and smooth transitions prevalent with colloidal chemists over the thought style of the "pluralists," the "analytical thinkers," and "dissectors" to whom understanding consists in the uncovering of diversity. Yet his main work followed the "pluralists" style: he contributed strongly to concepts of sharp specificity, through his immunochemistry as well as his work on human blood groups (for which he received the Nobel Prize). A thought style may have influenced Landsteiner's work, but it did not determine it. Capabilities seem to have been more important than a thought style. Because of his broad scientific education which included organic chemistry, he was able to create a very reliable and fertile new research program and maintain it even though the results contradicted his preferred thought style.
26. L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N Y, 1939.
27. A. E. Mirsky and L. Pauling, "On the Problem of Native, Denatured, and Coagulated Proteins," *Proc. Natl. Acad. Sci. U.S.A.*, **1936**, 22, 439-447. The idea that hydrogen nuclei formed a weak bond in organic compounds was suggested by Huggins in the Chemical Laboratory at the California Institute of Technology (W. M. Latimer and W. H. Rodebush, "Polarity and Ionization from the Standpoint of the Lewis Theory of Valence," *J. Am. Chem. Soc.*, **1920**, 42, 1419-1433).
28. Ref. 27.
29. Ref. 2, p 131.
30. Ref. 2, p 143.
31. Ref. 1, p 271.
32. Ref. 1; he lists as followers E. Baur, Panzer, H. von Euler, and Svanberg, who, except for von Euler, are largely unknown today.
33. R. Willstätter, "Zur Frage der proteinartigen Natur der Saccharase," *Ber. Dtsch. Chem. Ges.*, **1926**, 59 II, 1591-1594.
34. U. Deichmann and A. S. Travis, "A German Influence on Science in Mandate Palestine and Israel: Chemistry and Biochemistry," *Israel Studies*, **2004**, 9.2, 34-70.
35. J. B. Sumner, "The Isolation of the Enzyme Urease," *J. Biol. Chem.*, **1926**, 69, 435-441.
36. J. H. Northrop, M. Kunitz, and R. M. Herriott, *Crystalline Enzymes*, Columbia University Press, New York, 1948. Willstätter's international scientific authority as one of the most renowned German natural products chemist was such that biochemist Hugo Theorell, a Nobel laureate of 1955, assumed that the objections raised for many years in particular by Willstätter and his school against Sumner's and Northrop's work contributed to the fact that the Nobel Prize for the latter two was awarded only 20 years later, in 1946 (H. Theorell, "The Nature and Mode of Action of Oxidation Enzymes," in *Festschrift für Prof. Dr. Arthur Stoll zum siebenzigsten Geburtstag 8. Januar 1957. Arbeiten aus dem Gebiet der Naturstoffchemie*, Birkhäuser, Basel, 1957, 36).
37. Around 1900 chemists still assumed that proteins were large, crystallizable molecules; see, for example, F. N. Schulz, *Die Krystallisation von Eiweißstoffen und ihre Bedeutung für die Proteinchemie*, Fischer, Jena, 1901; *Die Größe des Eiweißmoleküls*, Fischer, Jena, 1903. The controversies in the history of protein research have been dealt with in detail in Ref. 1, 2, and 8. For research in Germany, including political aspects of the controversy, see also Ref. 13.
38. C. Tanford and J. Reynolds, "Protein Chemists Bypass the Colloid/Macromolecular Debate," *Ambix*, **1999**, 46, 33-51. These authors mention in particular Thomas B. Osborne in New Haven, CT, who through "compulsive attention to meticulous purification, reproducibility, error analysis, etc." was "head and shoulders above most of his contemporaries" (p 41).
39. Ref. 38 and Ref. 13, Ch. 7.1. Early other supporters of colloid chemistry include the protein chemists Ernst Waldschmidt-Leitz and, for several years, even renowned protein chemist Max Bergmann.
40. Wolfgang Ostwald to Wilhelm Ostwald, November 14, 1915, Wilhelm Ostwald Gedenkstätte Großbothen, file Wolfgang Ostwald.
41. For Wolfgang Ostwald's efforts in disciplinary building and his rise to the leading colloid chemist in Germany, see Ref. 13, Ch. 7.2.
42. J. W. Servos has reviewed Ostwald's lectures and his reception in the US (Ref. 11, pp 300-308).
43. Wolfgang Ostwald, *Die Welt der vernachlässigten Dimensionen, Eine Einführung in die moderne Kolloidchemie mit besonderer Berücksichtigung ihrer Anwendungen*, Steinkopff, Dresden, 1915, Vorwort and passim.
44. Ref. 43; the book appeared in the United States as W. Ostwald and M. Fischer, *An Introduction to Theoretical and Applied Colloid Chemistry: 'The World of Neglected Dimensions.'* John Wiley, New York, 1917.
45. Ref. 11, p 306.
46. P. J. Pauly, *Controlling Life. Jacques Loeb & the Engineering Ideal in Biology*, Oxford Univ. Press, New York, Oxford, 1987, 151-2.

47. As far as politics is concerned, it should be added that during the Nazi era, Wolfgang Ostwald, a member of the NSDAP, used chemical metaphors to describe euphemistically the expulsion of Jews. Between 1937 and 1941 he made several visits to England, the United States, Yugoslavia, Hungary, and Rumania, in which he made a determined effort to convince his audiences that the changes in Germany, i.e. the purge of Jews from German universities and society resembled a "recrystallization," necessary to gain purity. Returning from one of these travels, he reported to German authorities, "As chemists they understood me best when I spoke about our renewal as of a 'recrystallization' that is purification, stabilization, and restructuring." ('Rekristallisation', d.h. Reinigung, Stabilisierung, Neuformung); Wolfgang Ostwald to the German Research Council in reports about his journeys, (Ref. 13, p 390, translation by the author).
48. Ref. 13, Ch. 1.
49. J. Loeb, *Proteins and the Theory of Colloidal Behavior*, McGraw-Hill, New York, 1922.
50. J. Loeb, "Die Erklärung für das kolloidale Verhalten der Eiweißkörper," *Naturwissenschaften*, **1923**, *11*, 213-221(translation by the author).
51. For details of the disputes in Germany see Ref. 13, Ch. 7.2.
52. It is worth mentioning that Herbert Freundlich, a colloid chemist at the KWI for Physical Chemistry, conceded that Loeb's conclusion as far as proteins were concerned was probably right and that, in any case, all further research on proteins had to be based on it (H. Freundlich, "Jacques Loeb und die Kolloidchemie," *Naturwissenschaften*, **1924**, *12*, 602-3).
53. Ref. 6, pp 107-138.
54. Two other contributions to the physical chemistry of proteins were of crucial importance for their work, the Debye-Hückel theory of the behavior of ions in relation to their charge and radius, other ions and the dielectric properties of the environment, and Niels Bjerrum's demonstration of the Zwitterion (dipolar ion) state of amino acids in their isoelectric state (Ref. 2, pp 205-6).
55. E. J. Cohn and J. T. Edsall, *Proteins, Amino Acids and Peptides as Ions and Dipolar Ions*, Reinhold Publishing Corp., New York, 1943.
56. The disputes about the existence and properties of macromolecules in Germany in the 1920s have been tackled in detail by Priesner, who also analyzed the ensuing polemic between Staudinger and Hermann Mark and Kurt H. Meyer (Ref. 7d); see also Ref. 7e, Ch. 2, and Deichmann, who focused on the disputes about Staudinger and macromolecules during the Nazi era ((Ref. 13, Ch. 6.1.2 and 7.3).
57. H. Staudinger, "Über Polymerisation," *Ber. Dtsch. Chem. Ges.*, **1920**, *53*, 1073-1085.
58. K. Freudenberg, "Zur Kenntnis der Cellulose," *Ber. Dtsch. Chem. Ges.*, **1921**, *54*, 767-772.
59. H. Staudinger, "Über die Konstitution des Kautschuks (6. Mitteilung über Isopren und Kautschuk)," *Ber. Dtsch. Chem. Ges.*, **1924**, *57*, 1203-1208. During the following years Staudinger published a large number of articles in which he developed and expanded the view that there are large molecules which consist of many subunits held together by covalent bonds and defended the term macromolecule; for example, H. Staudinger, "Über die Konstitution der hochmolekularen Stoffe," *Naturwissenschaften*, **1929**, *17*, 141-144.
60. Staudinger described the opposition he faced in particular by organic chemists in Ref. 7b, pp 77-79.
61. Ref. 7e, pp 69-73.
62. Ref. 7e, p 74.
63. Ref. 7d.
64. K. H. Meyer and H. Mark, "Über den Bau des kristallisierten Anteils der Cellulose," *Ber. Dtsch. Chem. Ges.*, **1928**, *61*, 593-614.
65. K. H. Meyer, "Neue Wege in der organischen Strukturlehre und in der Erforschung hochpolymerer Verbindungen," *Z. Angew. Chem.*, **1928**, *41*, 935-946.
66. H. Staudinger, "Über hochpolymere Verbindungen, 140. Mitteil. Zur Entwicklung der makro-molekularen Chemie. Zugleich eine Antwort auf die Entgegnung von K. H. Meyer und A. van der Wyk," *Ber. Dtsch. Chem. Ges.*, **1936**, *69*, 1168-1185. The editorial board added that it considered the dispute between Mr. Staudinger and Mr. Meyer to be over.
67. Ref. 13, p 405.
68. For details see Ref. 13, Ch. 7.3.
69. E. Hammarsten, "Zur Kenntnis der biologischen Bedeutung der Nucleinsäureverbindungen," *Biochem. Z.*, **1924**, *144*, 383-466.
70. Loeb papers, Library of Congress, Manuscript Division, Michaelis to Loeb, March 4, 1921.
71. Michaelis' application for a professorship at the University of Lund (in 1920) was rejected on the grounds that he did not work on colloid chemistry, a predilection which, according to Jacques Loeb, was not shared in the United States at the time, where scientists like "Lawrence Henderson, Van Slyke, or Levene have not much respect for colloid chemistry left" (Loeb to Michaelis, Jan 27, 1921, Loeb papers, Library of Congress, Manuscript Division).
72. F. Lipmann, in H. Krebs and F. Lipmann, "Dahlem in the Late Nineteen Twenties," in H. Kleinkauf, H. von Döhren, and L. Jaenicke, *The Roots of Modern Biochemistry. Fritz Lipmann's Squiggle and its Consequences*, de Gruyter, Berlin, New York, 1988, 119 (translation by the author).
73. Ref. 2, p 159.
74. Ref. 5, p 380.
75. These criteria, proposed by Alvin Goldman and further developed for scientific research by Paul Thagard and Ulrich Charpa, comprise the reliability, relevance, efficiency, and fertility of a research practice (see, for example, P. Thagard, "Collaborative Knowledge," *Nous*, **1997**, *31*, 242-261).

76. L. Pauling, "Fifty Years of Progress in Structural Chemistry and Molecular Biology," *Daedalus*, **1970**, 99 (4), 988-1014 (1010).

### ABOUT THE AUTHOR

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*Mitmachen, Vergessen. Chemiker und Biochemiker im Nationalsozialismus* (2001), co-editor of *Jews and Sciences in German Contexts* (2007) and *Max Delbrück and Cologne. An Early Chapter of German Molecular Biology* (2007), and author of many articles in the history of biology and chemistry. She is recipient of the Ladislaus Laszt Award of Ben Gurion University of the Negev in Beer Sheva, Israel (1995) and of the Gmelin Beilstein Medal of the *Gesellschaft Deutscher Chemiker* (2005).

## The Partington Prize 2008

The Society for the History of Alchemy and Chemistry has established the Partington Prize in memory of Professor James Riddick Partington, the Society's first Chairman. It is awarded every three years for an original and unpublished essay on any aspect of the history of alchemy or chemistry. The prize consists of three hundred and fifty pounds (£350).

The competition is open to anyone with a scholarly interest in the history of alchemy or chemistry who, by the closing date of 31 December 2007 has not reached 35 years of age, or if older has completed a doctoral thesis in the history of science within the previous three years. Scholars from any country may enter the competition, but entries must be submitted in English and must not have been previously submitted to another journal. The prize-winning essay will be published in the Society's journal, *Ambix*. One hard copy of the entry, word processed on one side of the paper, should be submitted, along with a copy of the entry on disc. We prefer files to be in Microsoft Word 2000, if possible. Essays must be fully documented using the conventions used in the current issue of *Ambix*. Essays must not exceed 10,000 words in length, including references and footnotes. All entries must be submitted with a word count.

All entries should be sent to Dr Gerrylynn K. Roberts, Department of the History of Science, Technology and Medicine, The Open University, Walton Hall, Milton Keynes, MK7 6AA, UK, with the words "Partington Prize" written clearly on the envelope. Each entry should contain a **separate** title page giving the author's name, institution, postal address, email address and date of birth (and if relevant the date of completion of their thesis). The author's name and contact details **must not** appear on the pages of the essay as the identity of the author will not be made available to the judges. Essays (no more than one from each competitor) must be received no later than 31 December 2007.

The decision of the judges appointed by the Council will be final. The Society reserves the right to divide the prize between two or more entries of equal merit, or not to award a prize should no essay be deemed of suitable standard.

The name of the winner will be announced by 30 April 2008, and all essays will be returned to competitors soon after that date.