

A Brief History of *The Journal of General Physiology*

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On the occasion of the appearance of the complete online archive of articles published in *The Journal of General Physiology*, it seems timely to summarize briefly the developments that led to *The Journal* being founded and its subsequent history. In doing so I rely on the writings of Jacques Loeb, conversations with my predecessor, Paul F. Cranefield, and the following sources: Corner (1965); Pauly (1987); and Stapleton (2004).

The Journal of General Physiology was founded in 1918 by Jacques Loeb (1859 to 1924), who at the time was a Member of The Rockefeller Institute for Medical Research. Loeb had been recruited to The Institute in 1910 by Simon Flexner, The Institute's first Director, to establish a Laboratory of Experimental Biology. This decision by Flexner, a former student of Loeb, marked an important turning point because it signified a prescient broadening of The Institute's mission, from more clinically inspired medical research to biomedical research, defined broadly, with the ensuing emphasis on mechanisms. Indeed, Loeb's appointment was met with some initial resistance from The Institute's Board of Directors, and Loeb himself was concerned that The Institute's mission might constrain his freedom to pursue the wide range of problems that he was working on. Loeb wrote, in a letter to Flexner, that "... A research position is of course my ideal; the question is whether or not the [Rockefeller Institute] desires to add a new department namely that of Experimental Biology—the latter on a physico-chemical instead of a purely zoological basis. In my opinion experimental biology—the experimental biology of the cell—will have to form the basis not only of Physiology but also of General Pathology and Therapeutics . . ." (Osterhout, 1928). In the end, Flexner's leadership and vision overcame the reservations expressed by The Board of Directors and satisfied Loeb's concerns.

Loeb is arguably one of the most important scientists in the history of The Institute. His broad knowledge and interests served to inspire and motivate numerous investigators, and he was the model for Max Gottlieb in Sinclair Lewis' *Arrowsmith*. When Loeb arrived at The Institute, he already had made seminal contributions toward understanding numerous important questions: heliotropism (response to light) in animals and plants; visual perception; geotropism (response to gravity) and the control of body movements by the cerebral cortex;



Jacques Loeb, editor of *The Journal of General Physiology* 1918–1924.

tissue development and growth, including heteromorphosis (the transformation of one organ into another by suitable external manipulations); cellular growth responses to electric fields; the effect of extracellular electrolytes on cellular excitability; and oxidative metabolism. Loeb was recognized in particular for his contributions to artificial parthenogenesis, the ability of unfertilized eggs to develop into mature organisms. He was able to initiate this development by manipulating the extracellular electrolyte composition and osmolality. He further was able to increase the, normally quite limited, lifespan of the unfertilized egg by manipulating the egg's oxidative metabolism or extracellular environment. Consequently, Loeb concluded that fertilization and development should be viewed as physico-chemical events.

In 1902, Loeb moved from the University of Chicago, where he was professor of physiology, to the University of California, Berkeley, where he assumed the newly created position of professor of physiology with responsibilities both in Berkeley and the University's medical school in San Francisco. This relocation caused Russell Chittenden, President of the American Physiological Society, to remove Loeb from the editorial board of the

American Journal of Physiology because Loeb “no longer represented a ‘major’ institution.” Loeb responded by refusing to publish in the *American Journal of Physiology*; the controversy caused a revolt among the Society’s members, forcing Chittenden to step down as President. At Berkeley, Loeb established a Marine Biological Laboratory in New Monterey (between Monterey and Pacific Grove) close to Stanford University’s Hopkins Marine Station, at the location that a decade later would become John Steinbeck’s Cannery Row. While at Berkeley, he continued his studies in artificial parthenogenesis, tissue and organismal development, and the role of extracellular electrolytes on excitable and non-excitable cells, with an increasing emphasis on the underlying mechanisms, which Loeb strived to express in molecular terms using quantitative models. Indeed, “His notion of biological research was simple: all the observed phenomena should be expressed in the form of equations containing no arbitrary constants. Anything short of this is to be regarded as merely preliminary” (Osterhout, 1928, p. liii).

The term *General Physiology* seems to have been coined by Claude Bernard in 1885, who described “general physiology” as “the study of phenomena common to animals and plants” (Loeb, 1897; Davson, 1970). Loeb had already commented on the concept and its history in the 1890s (Loeb, 1897, 1898), where he stated that “general physiology is identical with an energetics of life processes.” Shortly thereafter he emphasized the importance of comparative physiology and physical chemistry as tools in physiological research in a key address that he introduced as follows, “If it be true that the fundamental problem of Physics is the constitution of matter, it is equally true that the fundamental problem of Physiology is the constitution of living matter. I think the time has come for Physiology to return to this fundamental problem” (Loeb, 1898). The move to Berkeley was instrumental in Loeb’s own development in this direction. First, he met Winthrop V.J. Osterhout, who had established a research program in botany with special emphasis on the electrolyte and volume regulation of marine plants, and who was thinking along similar lines as Loeb. Second, many physicists and physical chemists (e.g., Svante Arrhenius, Ludwig Boltzmann, Wilhelm Ostwald, and Ernest Rutherford) visited Berkeley, often staying with Loeb and his wife, and usually for lengthy periods, which encouraged extensive interactions. Though Loeb and Osterhout had many scientific interactions, they do not appear to have published together; but their joint scientific interests flourished at Berkeley, until budget cutbacks caused Osterhout to leave for Harvard and Loeb for the Rockefeller Institute.

As Loeb’s (and Osterhout’s) research became increasingly quantitative and aimed at elucidating underlying mechanisms, the question arose of what would be

an appropriate venue for the articles that resulted from their research. For a time, Loeb could solve the problem by publishing in German journals. Of the 217 articles that Loeb published from 1892, shortly after he arrived at Bryn Mawr College for his first faculty appointment in the United States, through 1913, only 83 were published originally in English (a complete list of Loeb’s publications was compiled by Kobelt, 1928) Between 1899 and 1902, he published extensively in the *American Journal of Physiology* (10 articles); but, as already mentioned, his relations with the *American Journal of Physiology* soured after he left Chicago for Berkeley. Though the *Journal of Biological Chemistry*, the *Proceedings of the Society for Experimental Biology and Medicine*, and *Science* were able to pick up some of the slack, Loeb’s primary journals were *Archiv für die gesamte Physiologie*, and to a lesser extent, *Archiv der Entwicklungsmechanismen der Organe* and *Biochemische Zeitschrift*. The situation changed abruptly with the outbreak of World War I. Loeb was adamantly opposed to the German war effort—he blamed the war on “unrepresentative governments,” but he was particularly disturbed by biologically grounded expressions of chauvinism among some German scientists (Pauly, 1987, pp. 131 and 144), which caused him to boycott German journals.

Now what? Loeb published a further 153 articles and reviews between 1915 and his death in 1924; only two of them were published in German. With the *American Journal of Physiology* being “off limits” (one can only wonder how things might have evolved if Chittenden had not removed Loeb from the *American Journal of Physiology*’s editorial board), Loeb decided to explore the creation of a new journal, which would have as its mission to elucidate basic biological mechanisms of broad physiological significance using the tools of chemistry and physics. But, though the proximate cause for founding *The Journal* was World War I, Loeb and Osterhout seem to have discussed the general notion for some time, presumably dating back to their time together at UC Berkeley. Loeb was able to secure support from the Rockefeller Institute, and in 1918 the formation of *The Journal* was announced:

ANNOUNCEMENT
OF
THE JOURNAL OF GENERAL PHYSIOLOGY

The Journal of General Physiology is intended to serve as an organ of publication for papers devoted to the investigation of life processes from a physico-chemical view-point.

As the constitution of matter is the main problem of physics and physical chemistry so the constitution of living matter is the main problem of general physiology, and in both cases the method of quantitative experimentation is needed.

Under the pressure of demands of medicine and other professions, physiology has developed in the direction of an applied science, with limited opportunity for the inves-

tigation of purely theoretical problems. On the other hand, the physico-chemical methods of analyzing life phenomena have thus far made little inroad into the domain of zoology and botany. Under these circumstances, it has happened that what might be regarded as the most fundamental of all the biological sciences, namely general physiology, has not come to have a journal of its own. It is this condition which the establishment of *The Journal of General Physiology* is intended to correct.

The editors of the *Journal* are Dr. Jacques Loeb, The Rockefeller Institute for Medical Research, New York, and Prof. W. J. V. Osterhout, Harvard University, Cambridge, Massachusetts.

The editors invite contributions relating to the physico-chemical explanation of life phenomena, no matter in what field of science they originate.

The Journal of General Physiology was not Loeb's preferred name for the new journal. During their discussions, Loeb and Osterhout had come to the conclusion that the new journal's intended mission would be described best if it were called *The Journal of Physico-Chemical Biology*! This proposal did not go over well with Simon Flexner, The Institute's Director, who was concerned that it would be considered to be a step too far from The Institute's mission.

As an aside, *The Journal of General Physiology* was not the first journal associated with The Institute. Thanks to the foresight of Simon Flexner, both *The Journal of Experimental Medicine* (founded in 1896 by William H. Welch at Johns Hopkins Medical School) and the *Journal of Biological Chemistry* (founded in 1905 by Christian A. Herter at Columbia University's College of Physicians and Surgeons) were nurtured through critical periods by The Institute. In fact, in 1904, Simon Flexner accepted the responsibilities as editor of *The Journal of Experimental Medicine* and The Institute became the sponsor of the journal, which led to the formation of the Publications Department in 1910 (renamed The Rockefeller University Press in 1958). Subsequently, the Publications Department was the publisher of the *Journal of Biological Chemistry* between 1914 and 1925, when the journal was turned over to American Society of Biological Chemists (now the American Society for Biochemistry and Molecular Biology). Later, two other journals were founded by The Institute (or The Rockefeller University): *The Journal of Biophysical and Biochemical Cytology*, later renamed *The Journal of Cell Biology*, was founded in 1955; and *The Journal of Lipid Research* was founded in 1960 and turned over to the American Society of Biological Chemists in 1973. Two other journals were, for a period, published by The Rockefeller University Press: *The Journal of Clinical Investigation* was founded by members of The Institute in 1924 and published by The Press between 1967 and 1999; and the *Biophysical Journal* was founded in 1960, with Frank Brink, Jr., of The University as the first editor, and published by The Press through 1993.

From 1918 through 1966, six issues of *The Journal of General Physiology* were published per year (September, November, January, March, May, and July). In the first volume (September 1918 to July 1919), 64 articles were published; the total number of published pages was 745, for an average length of ~12 pages (with ~400 words/page). By comparison, in 2004, *The Journal* published 99 regular articles (plus 14 Commentaries and 2 Milestones in Physiology); the total number of published pages was 1,534, for an average length of ~15 pages (with ~1,000 words/page).

The first manuscript received for publication (on June 20, 1918) was by A. R. Moore (from Rutgers College, New Brunswick, NJ) entitled "Reversal of reaction by means of strychnine in planarians and starfish." The last manuscript in the first issue, by Alice M. Boring and Thomas H. Morgan (from Peking Union Medical College, which has historical connections to the Rockefeller Institute, and Columbia University, New York, NY) entitled "Luteal cells and hen feathering" was received for publication on August 7; the issue was published on September 20, 1918, with an average time from receipt to publication of a little less than 10 weeks. Not bad, even by today's standards.

Not surprisingly, of the 64 articles in Vol. 1, 18 were authored or coauthored by either Loeb or Osterhout (9 each). Loeb's articles were all single-author contributions covering problems as varied as "amphoteric colloids" (five articles); "the influence of electrolytes on the electrification and the rate of diffusion of water through collodion membranes;" "the law controlling the quantity of regeneration in the system of *Bryophyllum calycinum*" (a tropical plant that can propagate through plantlets on its leaves); and "the physiological basis for morphological polarity in regeneration" (two articles). Osterhout's articles were mostly single-author articles covering problems related to the respiration and membrane permeability of marine organisms. Interestingly, in light of *The Journal's* only recently abandoned policy against publishing methods articles, two of Osterhout's articles were methodological, describing methods for studying respiration (CO_2 production) and O_2 consumption, respectively. Two other articles, coauthored with A.R.C. Haas, focused on photosynthesis in marine organisms. Among the other articles in Vol. 1, L.J. Henderson (of Henderson-Hasselbalch equation fame), Wallace O. Fenn (who made major contributions toward the oxidative metabolism of excitable tissues and was editor of *The Journal* from 1926 until 1961), and E.J. Cohn (who was instrumental in developing methods for blood plasma fractionation during World War II) examined the effect of electrolytes on the viscosity of dough, and P. Lecomte du Nouy published the first description of his tension balance apparatus for measuring surface tensions.



Winthrop J.V. Osterhout, editor of *The Journal of General Physiology* 1918–1961.

In the next few years, until his death in 1924, Loeb published 61 articles in *The Journal*. All but three (with Moses Kunitz, Robert F. Loeb [Jacques Loeb's son] and John H. Northrop) were single authored and addressed problems as varied as the production of parthenogenetic frogs, quantitative theories of geotropism and regeneration based on mass action, and the physico-chemical properties of membranes and proteins. The latter constituted Loeb's major effort, where he made two important contributions. First, he provided insights into the basis for anomalous diffusion across charged membranes, in which water moves in a direction opposite to that predicted from simple osmotic arguments, which he attributed to the charge on the membrane, which had an effect on the ions' permeability (1919–1920). Second, he reported the existence of Donnan potentials (1921). Loeb seems to have been the first to realize that Donnan's theory of membrane equilibria implied the existence of a potential difference across a membrane separating two electrolyte solutions, one of which contained impermeant proteinate ions. He measured these potentials and demonstrated that the measured potentials were in accord with the predictions of Donnan's theory. Loeb, however, did not recognize that Gibbs' thermodynamic description of phase equilibria implied the Donnan distribution; this insight can be traced to another physiologist, G.S. Adair at Cambridge University (Edsall, 1992).

When Loeb died in 1924, the baton was passed to Osterhout. Though Loeb and Osterhout were coeditors, Loeb appears to have been the first among equals because Osterhout introduced the term "Founded by

Jacques Loeb" on the masthead of Vol. 7 in 1924. Osterhout was recruited to The Institute from Harvard in 1925, and he served as editor until 1961. Osterhout asked William J. Crozier, associate professor of general physiology at Harvard, and John H. Northrop, one of Loeb's assistants (they published six articles together) who had been associated with The Institute since 1915, to join him. This triumvirate served as editors for more than 20 years until Wallace O. Fenn joined them in 1946.

Osterhout published a total of 120 articles in *The Journal*, the last one in 1956. As was the case for Loeb, most articles were single authored; they focused on questions relating to the membrane permeability properties and electrical excitability of aquatic plants, where he exploited fully the unique advantages provided by giant marine plant cells in *Valonia* and *Halicystis*. His articles were rigorous and addressed key questions that have yet to be fully resolved, such as the behavior of water in heterogeneous systems; he contributed importantly to the theoretical description of solute movement across membranes.

Northrop also published a total of 120 articles in *The Journal*, the first in 1919, the last in 1968. His early articles focused on the purification and crystallization of enzymes. Northrop's contributions (together with those of Moses Kunitz at The Institute and James B. Sumner at Cornell University) were instrumental for the eventual acceptance that enzymes were proteins, and that proteins were molecules with defined properties. Among his later contributions, he isolated and purified bacteriophages from *Escherichia coli* and demonstrated that they were composed of nucleic acids and protein (21:335–366). Northrop received the Nobel Prize (together with James B. Sumner and Wendell M. Stanley) in 1946 for his work on enzyme purification. He also was interested in membrane permeation and osmosis; his later interest in bacteriology is evident already in the 1920s, when he worked with Paul H. de Kruif. He published his first article on bacteriophages in 1930; but it was not until the late 1940s that he fully focused on bacteriology and virology, and, in particular, on lysogenic bacteriophages. Roger M. Herriott published a biographical sketch of Northrop (Vol. 45, issue 4/2:1–16).

Crozier published a total of 119 articles in *The Journal*, the first in 1919, the last in 1950. Though Crozier never worked with Loeb, much of Crozier's early work (on geotropism and heliotropism) was based on Loeb's earlier contributions. His later work focused on visual perception in animals.

Unfortunately, papers pertaining to *The Journal's* early history seem to have been discarded by Osterhout's widow after his death. According to Paul F. Cranefield, in his eulogy for Alfred E. Mirsky (64:131–133;



John H. Northrop, editor of *The Journal of General Physiology* 1924–1961.

1974), Loeb and Osterhout managed their responsibilities with no outside review. Manuscripts were passed back and forth between New York City and Cambridge, read by both editors and the decisions were made by consent. It is not clear whether Loeb and Osterhout communicated only in writing. New York and Boston were linked by telephone in 1883, and they could have discussed the manuscripts over the phone. The editorial practice becomes relevant when considering the enviably short time from receipt to publication noted above, which is feasible only if the editors do not need to badger tardy reviewers, or wait for equally tardy authors to return their revised manuscripts. There were hints of changes in the editorial decision making in 1924, beginning with Vol. 7, when Crozier and Northrop joined Osterhout as editors, and manuscripts no longer were “Received for publication” but rather “Accepted for publication” a phrasing that persisted through Vol. 22, 1938–1939. But the fundamental practice, that each manuscript was read by all editors, and the decision to accept or decline a manuscript by common consent of the entire board, persisted—even though the three editors were at three different locations: Crozier at Harvard in Cambridge, MA; Osterhout at The Institute in New York, NY; and Northrop at The Institute’s Department of Animal Pathology in Princeton, NJ. It is not clear how Loeb and Osterhout (and Crozier and Northrop) managed the conflicts that arose when manuscripts were submitted by the editors.

During the 1920s, *The Journal* fully lived up to its name. In addition to the editors’ contributions, the major themes were bacteriology, although bacteria not in-

frequently were regarded as complex colloids; phagocytosis and leukocyte biology, with contributions from Wallace O. Fenn; light reception and photochemistry, with major contributions by Selig Hecht; photoluminescence, with major contributions by E. Newton Harvey; physical chemistry of membranes and surfaces, with major contributions by Harold A. Abramson, David I. Hitchcock, and Leonor Michaelis; and the dielectric properties of biological membranes, with contributions from Hugo Fricke (who measured the red blood cell membrane capacitance, and suggested that the membrane was a thin, low-dielectric, and insulating sheet with a thickness of 33 Å) and Kenneth S. Cole. Among other articles, H. Keffer Hartline published what appears to be his first article on photoreception (6:137–152); Cecil D. Murray published his seminal work on vascular branching based on a minimal work principle (9:835–841); and Duncan A. MacInnes and Malcolm Cole published a glass electrode method for pH measurements in very small volumes (12:805). A Jacques Loeb memorial volume (Vol. 8) also appeared, but in a rather disorganized manner; issues 2–6 were published between 1925 and 1927; issue 1, with Osterhout’s essay and Nina Kobelt’s listing of Loeb’s publications, did not appear until 1928. The highlight of the volume was issue 6, with contributions from F.G. Donnan, O. Meyerhoff, S.P.L. Sørensen and K. Linderstrøm-Lang, D.D. van Slyke, and O. Warburg, among others.

The Journal’s focus did not change significantly during the 1930s. Physico-chemical studies on proteins, including enzyme kinetics, remained plentiful. As noted above, Northrop began his studies on bacteriophages. H. Keffer Hartline published much of his early work on photoreception in *Limulus*. L.R. Blinks described the voltage-dependent conductance changes in *Valonia ventricosa* (one of the first descriptions of voltage-dependent conductance changes). Alfred E. Mirsky published extensively on protein denaturation (beginning in the late 1920s); work that formed the basis for Mirsky’s and L. Pauling’s proposal that protein denaturation was due to a breakdown of some uniquely folded protein structure that was stabilized by hydrogen bonds (Mirsky and Pauling, 1936). E. Newton Harvey and Alfred L. Loomis published their early work on high-speed photomicrography of living cells (15:147–153). Robert Emerson and William Arnold published their seminal work on the separation of the photosynthetic reactions (15:421–436). George Wald began his studies on phototransduction in rhodopsin, much of which was published in *The Journal*. John D. Ferry, published his article on the “Statistical evaluation of sieve constants in ultrafiltration” (20:95–104), which introduced the term “capture radius,” the difference between the pore and particle radii, one of the first descriptions of

finite-size effects. Studies on the squid giant axon became increasingly plentiful after 1938, when C. Ladd Prosser (with A.H. Chambers) and K.S. Cole (with Howard J. Curtis) published their early contributions, just two years after J.Z. Young had described the large fibers in the squid stellar nerve. In 1939, Cole and Curtis published their seminal analysis of the transverse impedance of the squid axon during activity; Fig. 4 from that article is among the more frequently reproduced figures from *The Journal*. The companion article, by Cole and A.L. Hodgkin, characterized the membrane and cytoplasmic resistances of the squid axon. In 1939, Osterhout retired from The Institute, but he continued as editor of *The Journal*.

The Journal's scientific focus remained unchanged during the 1940s. Though Wallace O. Fenn (at the University of Rochester) joined Crozier, Northrop, and Osterhout as an editor in 1946, this event had little impact on *The Journal's* scope. As far as I can determine, the editorial decision making continued as in the past, with all editors reading each manuscript and reaching a consensus decision on whether or not to publish a manuscript. Maybe as a result of this, the time from "Receipt for publication" to publication had crept to ~16 weeks by the late 1940s (more detailed data are provided in the Editorial preceding this article). There continued to be a heavy emphasis on protein chemistry, as well as bacteriology and virology. Red blood cell articles became more numerous, with major contributions by Eric Ponder. Max Delbrück published what appeared to be his first articles on bacteriophages (Vol. 23, issue 5). Radioactive tracers were introduced by Wallace O. Fenn (together with R.B. Dean, R.R. Noonan, and L. Haege), who described the use of $^{42}\text{K}^+$ to measure the rate of K^+ uptake in red blood cells (24:353–365). Motivated by the availability of Moses Kunitz' report of crystalline ribonuclease (24:15–32), I. Fankuchen published initial x-ray crystallographic results (24:315–3166), and Fankuchen and J.D. Bernal published an exhaustive x-ray study of plant viruses (25: 111–165), which does not mention genes or DNA! Kenneth S. Cole published his description of the small-signal oscillatory response in the squid axon (25:29–51), and introduced a phenomenological inductance in the equivalent circuit, an idea that briefly was adopted by Hodgkin and Huxley before they began the voltage-clamp studies that led to their 1952 articles in the *Journal of Physiology*; and David E. Goldman published his celebrated analysis of the electrical properties of ion selective membranes, in which he introduced the constant field equation (27:37–60). Maclyn McCarty described the purification of DNA from beef pancreas (29:123–139), and Alfred E. Mirsky published his biochemical studies on chromosomes in *The Journal*. Reflecting World War II, a number of articles by,



Alfred E. Mirsky, editor of *The Journal of General Physiology* 1950–1961.

among others, Northrop, William H. Stein, and Roger M. Herriott described the biochemical effects of vesicants and mustard gases.

The 1950s were a period of significant changes. By 1951 Osterhout was in failing health, and Alfred E. Mirsky and Lawrence R. Blinks were asked to become editors. Mirsky soon after became the *de facto* editor in chief. Detlev W. Bronk and Frank Brink, Jr., became editors in 1953 and 1955, respectively, and Crozier retired as editor in 1955. In 1957 (Vol. 41), Mirsky enlarged the board of editors significantly by appointing six new editors in various fields. It remains unclear to me whether he instituted a formal peer review system using outside reviewers; Cranefield, writing about Mirsky and his contributions (Vol. 64, issue 2), implies that outside reviews became the norm sometime during the 1950s. In 1960 (Vol. 44), Mirsky completed the organizational changes: he became Editor (in chief); there were three associate editors; in order on the masthead they were David R. Goddard, Colin MacLeod, and Roy Forster, each with specific subject responsibilities; and 12 editorial board members. As seems to have become the tradition, Mirsky published extensively in *The Journal*; of the 57 articles that he published between 1925 and 1969, 15 articles dealing with various aspects of protein synthesis were published while he was Editor.

The 1950s also were a period of change in *The Journal's* scientific focus. There was continued emphasis on protein chemistry and enzymology, but bacteriology was on the decline, though the number of articles on bacteriophages increased from 7 in the 1940s to 17 in the 1950s, with important contributions by A.D. Her-



Paul F. Cranfield, editor of *The Journal of General Physiology* 1966–1995.

shey (including the Hershey-Chase “Waring blender” experiment, 36:39–56, which somewhat surprisingly does not cite the work of Avery, MacLeod, and McCarty) and Gunther S. Stent. The tobacco mosaic virus was another object of study with contributions by Barry Commoner. Photosynthesis continued to be a topic, with contributions by both Arnold and Emerson. George Wald, in collaboration with Ruth Hubbard, explored the photochemistry of rhodopsin and the stereochemistry of the retinal moiety. Henry G. Kunkel and Arne Tiselius published their paper-chromatographic method for separating proteins (35:89–118).

As a harbinger of changes to come, Herbert S. Gasser, who was Director of The Institute between 1935 and 1953, and who was awarded the Nobel Prize for his work on single-unit recordings, published his first article (out of five) in *The Journal* in 1950. Interestingly, though Gasser served as editor of *The Journal of Experimental Medicine* during his term as director, he does not seem to have had any involvement with *The Journal* before Mirsky assumed the editorial responsibilities. Gasser’s students, David P.C. Lloyd (monosynaptic reflexes) and Lorente de Nó (effects of ionic changes on electrical excitability) began publishing in *The Journal* at about the same time. Another driving force promoting electrophysiology, both cellular and systems neurophysiology, was Detlev W. Bronk who became editor in 1953, at the time he assumed the responsibilities as director of The Institute. In any case, electrophysiological research began to figure more prominently, with contributions by Michael J.V. Bennett, George Eisenman and Donald O. Rudin, Harry Grundfest, and Paul

Mueller. H. Keffer Hartline and Floyd Ratliff published their classic studies on lateral inhibition in the *Limulus* eye. Carleton C. Hunt described the fluctuations in spinal motoneuron excitability and its implications for reflex strength (38:801–811). Carlos Eyzaguirre and Stephen W. Kuffler published their classic studies on the crayfish stretch reflex (Vol. 39, issue 1); and Theodore H. Bullock and Susumu Hagiwara published their first intracellular recordings from the squid giant synapse (40:565–577). Otto F. Hutter and Wolfgang Trautwein published their results on the autonomic nervous system’s effects on cardiac pacemakers (39: 715–733). Lorin J. Mullins noted that the ion selectivity of excitable membranes could result from the presence of channels with defined radii, where ion solvation by the pore walls would compensate for the energy barrier associated with ion dehydration as it enters the pore (42:817–829); he also seems to have been the first to propose that “membrane pores,” now ion channels, are not rigid but deformable. Transport studies became more numerous. The red blood cell was among the favorite experimental preparations, with contributions by Paul G. LeFevre, Arthur K. Solomon, and Daniel C. Tosteson. Thomas Rosenberg and W. Wilbrandt published their analysis of uphill transport by counter transport (41:289–296). Epithelial transport also became a frequent topic, with contributions by Alexander Leaf and Hans H. Ussing, among others, and Eugene M. Renkin published his analysis of filtration, diffusion, and sieving through porous membranes (38:225–243).

Further changes occurred in the 1960s. As noted above, the present editorial structure largely was in place beginning with Vol. 44 in 1960, with Alfred E. Mirsky formally becoming editor in chief for 1960–1961, when he was succeeded by Clarence M. Connelly, who served from 1961 to 1964. Connelly is unique among the editors, in so far that he never published an article in *The Journal*; subsequent editors have to some extent followed his example, as they have published only sparingly in *The Journal*. 1960 marked another major change, as that was the first time the statement “Edited in Cooperation with The Society of General Physiologists and Regarded as the Society’s Official Organ” appeared on the masthead. Though *The Journal* and The Society share a commitment to “General Physiology” they had evolved independently; The Society was formed in 1946, 28 years after *The Journal* was founded (a brief history of The Society’s early history can be found in Vol. 109, issue 4, pp. vii–ix). Until 1960, only two of The Society’s presidents, L.R. Blinks and W.D. McElroy, had served also as editors of *The Journal*. A former president, David R. Goddard, served as associate editor from 1960 to 1967; another former president, J. Woodland Hastings, professor of biochemistry at University of Illinois, served as Editor from 1964 to

1966. In 1966, Paul F. Cranefield was recruited to The Rockefeller University, to establish a laboratory of cardiac physiology and to assume the responsibilities as Editor of *The Journal*. Under Cranefield's leadership, *The Journal* was published in monthly issues, beginning with Vol. 50 (1966–1967), where the first five issues appeared bimonthly and the last six monthly. Beginning in 1968, *The Journal* was published in two volumes per year of six issues each (January–June and July–December) per year and the associate editor positions were eliminated. At least some of these changes resulted because Cranefield inherited such a large backlog of manuscripts that he requested Detlev W. Bronk (President of The Rockefeller University) to provide a special budget allowance, in order to have a clean slate moving forward. Cranefield was then the sole editor for the next 17 years. During the summers, Cranefield traveled through Southern Africa, where he was trailed by couriers bringing manuscripts back and forth between New York and wherever he was. Cranefield's travels were so extensive that he added the following sentence to Information for Authors: "Articles received in late July and in August may be delayed both in acknowledgment and in review."

The shift in the focus of the published articles, toward membrane transport and electrophysiology, which was taking place already in the 1950s became more pronounced during the 1960s. Genetic studies, e.g., on bacterial transformation and bacteriophages, continued to be published (Roger M. Herriott and John H. Northrop); but there was a definite shift toward a focus on ion transport across bacterial membranes (Stanley G. Schultz). Vol. 49, issue 6, 1966, was devoted to DNA and protein synthesis; but the emphasis by that time clearly had changed. Elliott Robbins and Alexander Mauro published their demonstration of the independence of the diffusion and hydrodynamic permeability coefficients in collodion membranes (43:523–532); and Ora Kedem and Aharon Katchalsky provided their physical interpretation of the phenomenological coefficients describing membrane permeability phenomena (45:143–179). L.J. Mullins and M.Z. Awad analyzed the role of the sodium pump in the control of the membrane potential (48:761–775); and Mullins and Frank J. Brinley, Jr., published their studies of active cation transport using internally perfused squid axons, which since then have become a preparation of choice for such studies. Epithelial ion and water transport figured prominently with major contributions by Peter F. Curran, Jared Diamond (the standing-gradient model for isotonic fluid transport appeared in Vol. 50, issue 8), Gerhard Giebisch, Alexander Leaf, Stanley G. Schultz, Guillermo Whittembury, and Erich E. Windhager. Some of the key articles elucidating Na^+ -driven cotransport mechanisms, which

form the basis for the oral rehydration therapy for infantile diarrhea in third world countries, were published in *The Journal* (e.g., Schultz and Zalusky, 47: 1043–1059). Red blood cell ion and water movement also were becoming increasingly prominent, with major contributions by Joseph F. Hoffman, Aser Rothstein, Arthur K. Solomon, and Daniel C. Tosteson. Tosteson and Hoffman published their analysis of red blood cell volume regulation in 44:169–194. Lowell E. Hokin and Mabel R. Hokin published their studies on the stimulation of phosphatidic acid and phosphoinositide turnover.

The most dramatic shift in emphasis during the 1960s, however, was the ascent in electrophysiological studies on the gating and ion selectivity of the currents underlying electrical excitability, and the pharmacological dissection of the currents. In addition to the contributions mentioned below, Mordecai P. Blaustein and John W. Moore were frequent contributors. Susumu Hagiwara began his studies on excitability, and later also excitation coupling, in barnacle muscle fibers (48: 141–162). T. Narahashi, J.W. Moore, and W.R. Scott showed that TTX was a specific blocker of the voltage-dependent sodium currents (47:965–974). In 1965, Vol. 48, issue 5 was dedicated to electrophysiological studies: Clay M. Armstrong (with Leonard Binstock) published the first of his articles on the effects of quaternary ammonium ions on squid axon potassium currents; W. Knox Chandler (with Alan L. Hodgkin and Hans Meves) published results on the effect of ionic strength (identified as changes in surface potentials) on the voltage dependence of sodium currents as well as the ionic selectivity of "the sodium-carrying system of the active nerve membrane (a.k.a. sodium channels); George Eisenman and Franco Conti described their results on ion permeation from the vantage point of Eisenman's theory of ion selectivity; and Dennis A. Haydon (with T. Hanai and Janet Taylor) published the first article on planar lipid bilayers in *The Journal*. Armstrong followed up his work on quaternary ammonium ions in 50:491–503; Bertil Hille soon after published his studies on sodium and potassium currents, and their modulation by pharmacological agents, Ca^{2+} and H^+ (50:1287–1302, 51:199–219, and 51:221–236). The articles by Armstrong and Hille heralded a new era in ion channel studies, which have been a mainstay of *The Journal* ever since. Studies on higher-order function also were published: Donald Kennedy published extensively on photoreception and synaptic activity in the crayfish; Howard L. Gillary studied the salt receptor in the blowfly (Vol. 50, issue 2). The filamentous fungus *Phycomyces* figures prominently, as a preparation to study light reception, with contributions by, among others, Edward S. Castle and Max Delbrück. Muscle contraction and mechanochemistry began to figure

more prominently, with contributions from Edmund H. Sonnenblick, Annemarie Weber, and Saul Winegrad, among others, and Vol. 50, issue 6 was devoted to contractile properties. Lipid bilayers appeared with increasing frequency from 1967 onward, with major contributions from Alan Finkelstein and Albert Cass, Daniel C. Tosteson, and Thomas E. Andreoli. The first single-molecule studies published anywhere (I believe), were single-channel experiments in planar lipid bilayers by Ross C. Bean et al. (53:741–757), who described the discrete current fluctuations through EIM (excitability inducing material, a bacterial outer membrane protein) channels.

Looking back, the changes that began, if imperceptibly, around 1950 were completed by 1970. Though the revolution that was brought about by the advances in molecular biology has had enormous impact on *The Journal*, the major questions that are the focus of today's articles were largely defined, if vaguely so, by the 1970s. As I went through the articles published in *The Journal* over the years, the articles published in the 1940s share many similarities with the articles published in the 1920s (after accounting for the general advances that took place in biological research). The articles published in the 1970s had fewer similarities with the earlier articles, due to the changes that had taken place in *The Journal's* focus, but they form the basis for much of the work that is published today, as evident from the citations. Indeed, a number of authors who published in *The Journal* during the 1960s continue to publish in *The Journal*, which means it is time to end this historical summary.

Again looking back, there seems to have been three critical periods in *The Journal's* evolution, with one of them occurring before *The Journal* was founded. As noted above, one can only wonder whether Loeb would have founded *The Journal* if he felt that the *American Journal of Physiology* was an acceptable venue for his work. Given his stature, he might have been able to institute changes in the *American Journal of Physiology* that would have obviated the need for *The Journal of General Physiology*, if the *American Journal of Physiology* would have agreed to publish articles on plant physiology. The second critical event was the outbreak of World War I, which made the German journals unacceptable as venues for Loeb's work. The third was the appointment of Alfred E. Mirsky as editor in 1950. Though a renowned biochemist, today Mirsky is remembered mostly for his opposition to the notion that DNA could be the carrier of genetic information. In 1950, *The Journal* was poised to move into several different directions; it could equally well have become a key venue for the next generation of articles on bacteriology and virology, along the lines of the Hershey-Chase article, as it could have become a key venue for electrophysiological articles.

TABLE I
Editors of The Journal of General Physiology (1918–2004)

1918–1924	Jacques Loeb
1918–1961	Winthrop J. V. Osterhout
1924–1955	William J. Crozier
1924–1961	John H. Northrop
1946–1961	Wallace O. Fenn
1950–1961	Lawrence R. Blinks
1950–1961	Alfred E. Mirsky ¹
1953–1961	Detlev W. Bronk
1955–1961	Frank Brink, Jr.
1957–1961	Vincent Allfrey
1957–1961	Jean Brachet
1957–1964	C.M. Connelly ²
1957–1961	Roger M. Herriot
1957–1961	W.D. McElroy
1957–1961	A.K. Solomon
1960–1967	Roy Forster*
1960–1967	David R. Goddard*
1960–1964	Colin MacLeod*
1964–1966	J. Woodland Hastings ³
1964–1967	Bernard C. Abbott*
1966–1995	Paul F. Cranefield ⁴
1984–	Olaf S. Andersen ⁵
1984–	David C. Gadsby*
1984–1995	Robert Shapley*
1996–	Angus C. Nairn*
1996–	Lawrence G. Palmer*
2002–	Kenneth Holmes*

* denotes associate editors.

¹Editor 1950–1960; Editor in Chief, 1960–1961.

²Editor 1957–1961; Editor in Chief, 1961–1964.

³Editor in Chief.

⁴Editor in Chief.

⁵Associate Editor, 1984–1995; Editor in Chief, 1995–present.

This state of affairs was not reached until the late 1960s, when Paul F. Cranefield, a bona fide electrophysiologist, was editor; but the major change in focus began to occur in the 1950s.

To ensure that *The Journal* continues to serve its mission, a number of developments have taken place since 1970. In 1984, Paul F. Cranefield asked Olaf S. Andersen, David C. Gadsby, and Robert Shapley to become associate editors, which in effect reestablished the editorial style that existed in the 1920s, with one important modification: that the editor and associate editors meet weekly to discuss the manuscripts based on the outside reviews and the editors' own evaluations, a practice that, with modifications, continues today. In 1995, Paul F. Cranefield stepped down as Editor after almost 30 years of service, being the sole editor for 17 years, and Olaf S. Andersen took on the responsibilities of Editor. Beginning with Vol. 107, 1996, Robert Shapley stepped down as associate editor, and Angus C. Nairn and Lawrence G. Palmer became associate editors; in 2002,

Kenneth Holmes became associate editor. Four new types of articles are published, in addition to the regular research articles: Commentaries on research articles; Perspectives that elucidate different facets of a problem; Brief Reviews; and Historical Milestones in Physiology. In contrast to most other journals, the editorial decision making has not been decentralized, the decisions (at least the difficult ones) continue to be consensus decisions by the editor and the associate editors, based on the input of outside reviewers. The decision letters are written by the editor or one of the associate editors, and signed by the letter writer.

The Journal's relations with The Society of General Physiologists have been strengthened in recent years, as Olaf S. Andersen and David C. Gadsby both have served as presidents of The Society and Lawrence G. Palmer is currently president-elect. *The Journal* and The Society remain distinct entities, however, and the Editor remains an appointment made by the President of The Rockefeller University.

Looking forward, the focus on mechanistic studies continues to put *The Journal* in a class by itself. The strong quantitative emphasis, which has been one of the defining characteristics of *The Journal*, continues. Importantly, it is not quantification for its own sake; it is to understand the biology properly because quantitative reasoning frequently provides the key insights that are needed to understand the biological problem that is under investigation. The direction (increase or decrease) of the measured changes in some experimental observables may be compatible with any number of different mechanisms; to distinguish among the possible underlying mechanisms, it becomes critical to know the magnitude (a factor of 3 vs. a factor of 10³) of the observed change. It thus becomes important to have well-developed models that allow for quantitative reasoning and the ability to distinguish among different plausible mechanisms. But no model is better than its underlying assumptions, which brings us back to Loeb's original choice of name for *The Journal*, *The Journal of Physico-Chemical Biology*. To understand the complexities of cellular and higher-order function, we need to define the underlying mechanisms in systems that allow for mechanistic/quantitative insights based on physical and physico-chemical analysis of the system at hand, not some oversimplified model that neglects essential physical constraints. The choice of experimental system thus becomes critical.

It is in this context exciting that we are in the midst of another transition. The era of the “well-mixed” cell is behind us. Signaling is punctate, and many important questions in cell signaling, including excitation-con-

traction and excitation–secretion coupling and other complex signal transduction events, such as mechanotransduction and light, smell, and taste sensation, need to be considered as (at least) four-dimensional processes that take place in a complex inhomogeneous geometry. Similar statements can be made with respect to muscle contraction and nonmuscle motility. We need to know the anatomy, whether molecular or cellular, including the identities of the interacting players; but function is dynamic, reflecting the energetics and kinetics of the numerous interacting elements that together underlie biological function. Progress therefore will depend on a thorough appreciation of the underlying biology and its complexity in conjunction with detailed mechanistic studies on carefully selected systems that allow for the insights necessary to understand the biology of interest. These studies depend on the physical biology and mechanistic reasoning that have been guiding *The Journal* through its various transitions and that will continue to do so. This has an associated cost, however, because many are uncomfortable with the quantitative/rigorous reasoning that defines general physiology as it appears on the pages of *The Journal*; the reward is that articles published in *The Journal* are timeless (as judged by their effective half-lives in citation statistics, which range between 9 and >10 years).

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