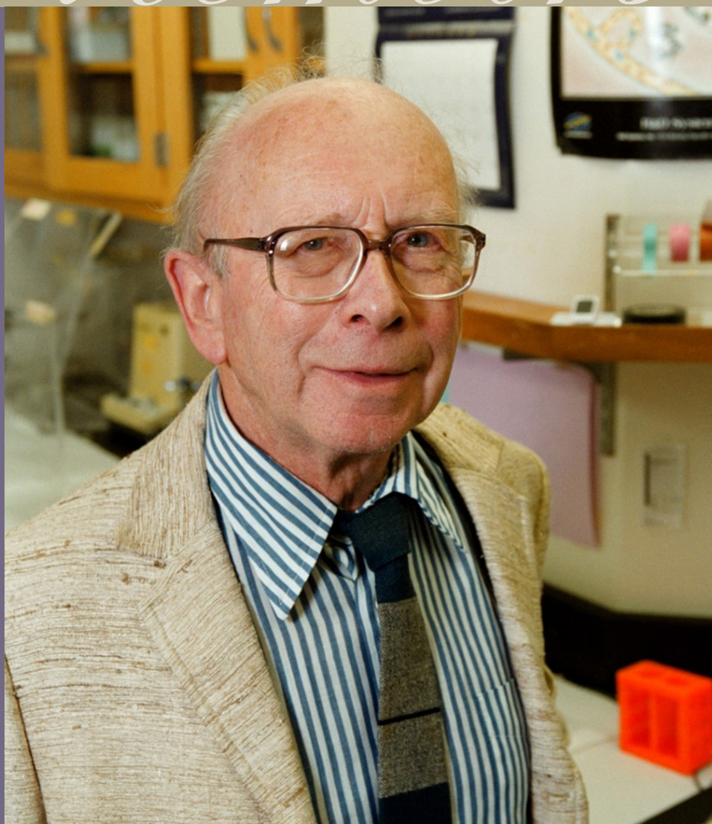
Arthur B. Pardee

1921–2019

BIOGRAPHICAL *Memoirs*



A Biographical Memoir by
Thoru Pederson
and Alfred L. Goldberg

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NATIONAL ACADEMY OF SCIENCES

ARTHUR B. **PARDEE**

July 13, 1921–February 24, 2019

Elected to the NAS, 1968

Arthur Pardee was a seminal figure in the modern era of biochemistry whose discoveries played a critical role in the development of molecular biology. He did pioneering work on feedback regulation and gene expression in bacteria, proposed the concept of an unstable intermediate between DNA and protein synthesis, subsequently identified as messenger RNA, and in his later career, made major contributions to understanding the cell cycle and the control of mammalian cell growth.

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By Thoru Pederson
and Alfred L. Goldberg

Early Life

Arthur Beck Pardee was born in Chicago on July 13, 1921, to Charles Arthur Pardee, a physician, and Elizabeth Beck Pardee. He attended public schools and developed a love of reading, art, music, the outdoors, and chess, excelling in the latter. He was athletic and skilled in swimming, diving, and fencing. In college, he was on a tournament-winning fencing team and was an enthusiastic tennis player well into his 80s. Although Pardee was self-propelled intellectually in his formative years, he emphasized that his interest in science was stimulated by his maternal grandfather, physician and medical researcher Emil Beck. Dr. Beck and his brothers had launched the North Chicago Hospital in 1906, modeling it on the Mayo Clinic. The Beck family knew the Mayo brothers and other luminaries, including Albert Einstein, who visited their home on several occasions. Another important influence was his maternal great aunt, Ida Hyde, who was the first woman to receive a Ph.D. in the sciences from the University of Heidelberg. She later conducted research in neurobiology at the Marine Biological Laboratory in Woods Hole, Massachusetts, obtained an M.D. from Rush Medical College in 1911, and went on to become an eminent physiologist.

While completing his doctoral studies, Pardee married Marjorie Maxstadt in 1947 and they would have five children. Their son Michael has said of the home in El Cerrito north of Berkeley that it was "full of activity, including frequent dinners and musical quartets with friends, students and colleagues, a growing young family, Asian art, good food, and California wines."(1) Pardee was a cellist and a lifelong devotee of chamber music.

Education and Training

Pardee received his B.S. degree in chemistry from the University of California, Berkeley (UCB) in 1942. There he had his first significant experience in research, working in the laboratory of photosynthesis pioneer and later Nobel laureate Melvin Calvin. After college, he entered the California Institute of Technology (Caltech), where he worked toward his Ph.D. on antibody specificity(2) with another scientific luminary, Linus Pauling, whom he always admired as one of the giants of twentieth-century science. His graduate studies were unfortunately interrupted by World War II, during which he became involved in weapons-related military research on the toxicity of uranium and certain gases. The death of his mother from cancer led to a desire to work on metabolic derangements in tumors. Therefore, after receiving his Ph.D. in 1947, he joined the laboratory of Van Rensselaer Potter at the University of Wisconsin, where he worked on the enzymology of the tricarboxylic acid cycle, publishing six significant papers in 22 months on the metabolism of normal cells and tumors. In one of these papers, he and Potter analyzed how oxaloacetate can inhibit an earlier enzyme in the cycle, succinic dehydrogenase.(3) It seems likely that through this work, Pardee first became interested in the novel idea that downstream products can influence an upstream step in a metabolic pathway. As he later stated, "…there was feedback there, although those terms were not used [at the time]."(4)

Early Career

The complexities of mammalian cells and the cancer problem convinced Pardee to focus on the simpler and more tractable metabolism of bacteria. In 1949 he returned to UCB as an Assistant Professor of Biochemistry and a member of the Virus Laboratory. There he began to work on the effects of bacteriophage infection on host-cell metabolism and the possible interplay between the synthesis of nucleic acids and proteins. In an initial collaboration with his departmental colleague Howard Schachman, he provided the first evidence for the RNA-containing particles that later became known as ribosomes. From 1951 to 1953, Pardee focused on how phage infection alters the activities of host-cell

enzymes and leads to increased nucleic acid synthesis. These studies built on his finding that the synthesis of nucleic acids in *E. coli* depends on the availability of amino acids in the medium(5), an important discovery that led to recognition of what became known as the “stringent response.” A coupling between the synthesis of protein and nucleic acids had been postulated by others, but Pardee soon published another insightful paper in which he confirmed the hypothesis that de novo enzyme formation in some way depended upon the production of new nucleic acids.(6) This paper was probably his first to reach a large audience, and beyond the clarity of the results, it also illustrated the lucidity and elegance of his scientific writing, which colleagues would come to admire in the years ahead. This article illustrated his scholarly attention to describing fully earlier work, a parsimony in interpretation of results, and his uncommon skill in presenting novel ideas clearly.

In continuing to pursue the regulation of nucleic acid synthesis, Pardee focused on the biosynthesis of pyrimidine nucleotides. In 1956, in back-to-back papers with his post-doctoral fellow Richard Yates,(7, 8) he demonstrated definitive evidence for a feedback mechanism in which the end product, cytidine triphosphate, inhibited the first step in the pyrimidine biosynthetic pathway, the enzyme aspartyl transcarbamoylase, even though the end product has no structural similarity to the enzyme’s substrates. The concept of feedback regulation had achieved importance in engineering and physiology, but it had not entered yet into biochemical thought.(9) Slightly before the Yates and Pardee papers appeared, H. Edwin Umbarger(10) had also demonstrated end-product inhibition in the biosynthetic pathways for isoleucine and valine.(11) In a lecture at Umbarger’s retirement, Pardee generously characterized Umbarger’s paper as “remarkable” and stated, “Perhaps it was just as well that feedback inhibition was reported almost simultaneously in two different systems, and by two unconnected laboratories.”(12) As a result, within a few years, feedback inhibition of the first step in biosynthetic pathways became firmly established as a general mechanism controlling the production of amino acids and nucleotides.

Feedback inhibition became one of the unifying principles in understanding intermediary metabolism and explained, in Pardee’s words, how “living organisms usually produce their constituent molecules to meet their needs, no more or less.”(13) But the underlying mechanisms for such regulation remained unclear until a brilliant student in Pardee’s lab, John Gerhart, made the critical insight. Working with purified aspartate transcarbamoylase, Gerhart observed that the feedback inhibition by CTP was lost upon enzyme storage or heating, but neither reduced its catalytic activity. They thus demon-

strated that the enzyme's catalytic site was distinct from that where the inhibitory end product binds.(14) This penetrating discovery ignited the entire field of enzyme regulation. The idea that an intracellular ligand could change a protein's functional properties had of course been known from classic studies on hemoglobin, where the ligand, oxygen, enhances the affinity for additional oxygen atoms, whereas carbon dioxide decreases affinity for oxygen. However, the finding that an enzyme's catalytic activity could be altered by a regulatory ligand in a physiologically important way was breathtakingly new.

When Gerhardt and Pardee made this major discovery, it was not yet known whether aspartyl transcarbamoylase contained a single polypeptide chain or was a multi-subunit enzyme. They later demonstrated that it was a complex of a regulatory (ligand-binding) subunit and a catalytic (substrate-binding) one, but for this breakthrough concept it of course didn't matter. Subsequently, the existence of multi-subunit complexes and large-scale structural changes induced by ligands became central themes of protein chemistry and enzyme regulation. Later, Jean-Pierre Changeux, JeffriesWyman, and Jacques Monod generalized this concept and coined the more daring term allostery. At that time they had no evidence for a change in shape of the enzyme, and a more rigorous term might have been alio loco. Years later Pardee said that he felt the Pasteur group had tried to simplify things too much in proposing the term allostery to describe the subunit interactions as a general mechanism, before much was known about the molecules involved. But he added "… the broad allosteric model was developed at the Pasteur, and I think it was a very splendid contribution."(4)The evolution of the concept of allostery by Gerhard and Pardee and by Monod's team at Pasteur has been dissected in meticulous detail elsewhere. (15)

The PaJaMo Experiment

There is little sense from Pardee's early career that he was obsessed by the gene itself; being trained in protein chemistry, he instead focused on how cells adapt to changing environments, leading him in due course to pioneering work on enzyme regulation. As in every new field he entered, he designed incisive experiments to not only describe cellular phenomena, but to also clarify the underlying biochemical mechanisms. His research had always exhibited insight in recognizing topics of fundamental import, and he did so again when the time for his sabbatical arose. Pardee had long followed the work of Monod's group at the Pasteur Institute, where incisive studies of bacterial physiology and phage genetics had revolutionized microbiology. Pardee recognized the advantages of joining this group for a year, and there in 1957 he conducted one of the most ingenious experiments in the history of molecular biology. In prior classic studies, Monod

and coworkers had described in *E. coli* the coordinate induction by lactose of both the key enzyme in lactose metabolism, β-galactosidase, and the downstream gene for lactose transport, terming these two genes the lac operon. They had also isolated various mutants that displayed constitutive expression of this operon. The question then arose as to how the supply of lactose to the bacteria could so very quickly affect the expression of the operon and what was the basis of constitutive enzyme expression in the mutants.

In a series of experiments conducted by Pardee and with one of the senior members of the host lab holding the stopwatch to follow the kinetics of enzyme induction, they discovered that inducibility by lactose was genetically dominant over the constitutive expression of the enzyme. This implied that in cells growing on glucose in the absence of lactose, the genes for lactose metabolism are repressed by the product of another regulatory gene, but this repression is released when lactose is provided to the cell.(16) This elegant experiment launched a transformative period in the understanding of the regulation of gene repression in bacteria and greatly influenced thinking about gene regulation in eukaryotic cells. Building on these findings, Monod and Jacob generalized this concept on gene repression to phage lysogeny, which eventually led to the isolation by others of the repressors of the lac operon and the bacteriophage lambda cI gene.

There have been many viewpoints on the respective roles of Pardee and the Pasteur group in this monumental study, widely called the PaJaMo experiment (for coauthors Pardee, Jacob, and Monod), and in the development of the concepts of repression and induction. Although the host investigators were distinguished microbial physiologists and geneticists, unlike Pardee, they were not biochemists oriented towards molecular mechanisms. Most likely, this collaboration was uniquely powerful owing to the combination of the biochemical insights of Pardee and the fertile groundwork on this system developed by the Pasteur group (vide supra).(15)

Messenger RNA

Upon his return to Berkeley, Pardee resumed his studies of phage infection on host cell metabolism and continued to think about linkages between nucleic acids and enzyme synthesis. In 1959 he published one of his most prescient yet most underrecognized papers.(17) In it, he put forth a compelling case that enzyme induction most likely involves an intermediate between DNA and the synthesis of a new enzyme, and that this intermediate was likely to be short-lived. This paper got little notice because it was published in a cell biology journal as part of the proceedings of a conference. He did not follow up by publishing these major findings in a regular research article. Subsequently,

the hypothesis of a short-lived intermediate was further supported when, with his student Monica Riley, he showed that continued synthesis of an enzyme required that the encoding gene remain intact.(18) Two years later, the existence of messenger RNA was directly demonstrated in bacteria after phage infection and during normal growth. Many, including some involved in those discoveries, credit Pardee as having formulated the key concept.

Princeton and the Transition to Mammalian Cells

In 1961, having spent his entire student and academic career in California, Pardee was lured to Princeton University in New Jersey. Jacques Fresco, a nucleic acid biochemist, had joined Princeton's Chemistry Department a year earlier and had successfully promoted the idea of a program in biochemical sciences. Pardee had become open to new opportunities, and his move to Princeton led subsequently to the establishment of the Department of Biochemical Sciences with him as Chair. He subsequently recruited Bruce Alberts, who had been Fresco's student at Harvard, and several other talented young investigators soon followed.

By the time Pardee arrived at Princeton, he had begun to think further about the regulation of cell growth not only in bacteria but also in mammalian cells. One influential scientific contribution during his Princeton years concerned the mechanisms of active transport of nutrients by bacteria. In studying sulfate uptake by *Salmonella typhimurium*, his lab discovered a class of high-affinity substrate-binding proteins in the periplasm that are critical for uphill transport of many nutrients and chemotaxis.(19, 20, 21) He also began to refocus his efforts to study mammalian cell growth and cancer biology, and his first forays, evolving from the bacterial transport work, were studies on how active transport of nutrients by mammalian cells relates to growth control.(22) At this time he also began to investigate protein expression during the mammalian cell cycle(23), work that foreshadowed a breakthrough technique he would later develop (vide infra).

In order to better prepare themselves for research on cancer, in 1972-73, Pardee and the distinguished geneticist Ruth Sager, took a sabbatical in the laboratory of Sir Michael Stoker at the Imperial Cancer Research Fund in London. Sager had done fundamental work on cytoplasmic inheritance and, like Pardee, had decided to refocus on cancer biology, with the London sabbatical leading her subsequently into the field of tumor suppressor genes. Drawing upon his sabbatical work, Pardee published a seminal paper postulating a "restriction point" in the G1 phase of the cell cycle.(24) The key concept was that there exists a time just before DNA replication when cells pause to consider

pivoting between proceeding through a further cycle or into growth arrest. Knowledge about the control of the cell cycle had been already advancing through the isolation of yeast mutants, and Pardee's concept complemented these developments. It became the focus of his many further studies, with his recognition that growth factors in serum regulate this step in normal cells, but in transformed cells serum factors have less influence owing to an impairment of the normal G1 to S regulatory system. This line of thinking empowered much of Pardee's remaining career.

Upon his return to Princeton from this sabbatical, Pardee continued to develop the "restriction point" concept as a key regulatory point in the cell cycle in both yeast and mammalian cells, while also concurrently continuing his earlier work on the sulfate-binding protein of *Salmonella*.

Harvard Years

In 1975, Pardee and Sager, now married, were recruited to the new Sidney Farber Cancer Center (later renamed the Dana-Farber Cancer Institute) in Boston. Pardee also became an active member of the Department of Pharmacology at Harvard Medical School. In addition to serving as Chief of the Division of Cell Growth and Regulation at the Farber, Pardee and Sager greatly enhanced that institution's eminence in basic science. Most importantly, they were critical in helping to attract and foster the work of talented younger faculty. One of these recruits, Charles Stiles, summarized Pardee's influence thus:

> *Today, the Dana-Farber Cancer Institute…is well-known and nationally ranked. However, it was small and unknown, at the onset—created de novo out of Richard Nixon's congressional 'War on Cancer.' The presence of Art Pardee lent instant credibility (both scientific and interpersonal) to basic research at this new initiative. From 1976 onwards into the oncogene era, many of our most successful basic scientists took the Farber job because of Art. (Personal communication of C.S. to A.L.G.)*

The move to Harvard constituted a smooth, logical continuity in Pardee's work, including exploration of how membrane transport differs in normal and cancer cells, how the overall synthesis of proteins changes during the cell cycle, and how protein turnover is at play in growth control.(25, 26, 27, 28) Yet another of Pardee's contributions at this time was the discovery that DNA replication is mediated by a large, multienzyme complex, which he named the "replitase."(29) An intriguing aspect of the finding was that this complex contained not only the DNA polymerase but enzymes related to

deoxyribonucleoside synthesis via enzymatic reductase of ribonucleosides, raising the possibility of a direct channeling of the precursors directly into the replicating DNA.(30, 31) Like so many of Pardee's findings and insights, this idea caught on and led others to further dissect the DNA replication machinery, leading to definition of the "replisome" that contains the DNA replication licensing factors that propel the cell from G1 into S, a tribute to Pardee's vision.

By the mid-1980s, Pardee's work had begun to move from mammalian cell growth control to the cancer problem and potential therapeutics that could be envisioned given the basic research that he and others had done. He had been thinking about this for years, having written a seminal perspective 1964 (32) and in 1987 delivering a major lecture on this theme with even deeper insights.(33) His laboratory commenced studies on how existing cancer drugs operated in terms of cell-cycle regulation, leading to a program of novel ideas and findings. It is interesting to look back and see how Pardee was focused on the metabolic vulnerabilities of cancers and how tumor cells evade the normal controls on cell-cycle progression. He was among the first to espouse this idea, and his laboratory made significant pre-clinical advances on this front.

Pardee's laboratory continued to publish leading work through the 1980s and 1990s on the ways in which cell-cycle progression controls are altered in cancer cells as well as how the actions of various chemotherapeutic drugs could affect the cell cycle. His group also continued to pursue the altered transport of nutrients and the actions of growth factors as keys to the cancer problem, while also delving more deeply into regulation of gene expression during the cell cycle. Flowing directly out of these studies, in 1992 he and Peng Liang introduced a transformative method, termed "differential display," to define the entire population of messenger RNAs in a cell or tissue.(34) Their goal was to understand the spectrum of changes in gene expression in cancer and during each stage of the cell cycle. At the time, methods to identify the population of messenger RNAs were laborious. Differential display reduced the time and cost by orders of magnitude and was widely adopted to define the changes in mRNA in response to external signals, in disease, and during differentiation. It also allowed mRNAs of particular interest to be isolated and cloned. Eventually, this approach was supplanted by other gene array methods, but it was a transformative technological advance at the time and illustrates Pardee's insight in recognizing the importance of such global information, long before the era of genomics and systems biology.

During the final phase of his career, Pardee focused increasingly on cancer vulnerabilities and chemotherapeutic mechanisms, and he also interacted with other groups at the Dana-Farber Cancer Institute, including clinical colleagues.(35) At the time of his death he was engaged in the emerging cancer stem cell field with his student, subsequent friend, and colleague Chiang J. Li.(36) Pardee worked continuously, maintaining an active laboratory into his late years. In fact, he developed the differential display method in his late seventies. Into his early 90s, his productivity only slightly and at his 97th birthday party he had on hand preprints of his latest article to give to friends.(37, 38)

Recognitions

Pardee received many honors for his major contributions to our understanding of biochemical regulatory mechanisms and cell growth, including election to the National Academy of Sciences (USA), the National Academy of Medicine (formerly the Institute of Medicine), the American Academy of Arts and Sciences, and the American Philosophical Society, a honorary doctorate from Sorbonne University and an honorary professorship from Southeast University in Nanjing, China. His many major awards included the Paul Lewis Award of the American Chemical Society, the Krebs Medal of the Federation of European Biochemical Societies, the Rosenstiel Medal from Brandeis University, the 3M Award of the Federation of the American Societies for Experimental Biology, the Boehringer Mannheim Molecular Bioanalytics Prize, the Distinguished Alumni Award of the California Institute of Technology, and the Princess Takamatsu Prize of Japan. A clear indication of the esteem and affection of colleagues was his election to the presidencies of both the American Society of Biochemistry and Molecular Biology and also the American Association of Cancer Research.

Despite his major scientific achievements and many honors, Pardee was always remarkably approachable, gracious, soft spoken, and modest in dealing with others. He also stood out in nurturing the careers of his trainees, many of whom have gone on to distinguished independent scientific careers. Recently, three of his former trainees described how they “treasured his mentorship. He created a fabulous environment in which to train where everyone worked together and where the goal is to have fun discovering new biology.”(39)

Pardee was predeceased by his first wife and two of their five children, and by Dr. Sager. The last twenty years of his life in Cambridge and summers in Woods Hole were enriched by his wife, Ann B. Goodman, who shared his boundless curiosity, broad intellectual interests, and passion for Asian art and classical music. Pardee died in his sleep

on February 24, 2019, at the age of 97. In reflecting on his career in 2005, he quoted Confucius, “Choose a job you love, and you will never have to work a day in your life.”

Arthur Pardee will long be remembered as a brilliant, but humble visionary biochemist, an engaging and caring colleague, and a powerful embodiment of science for the common good.

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