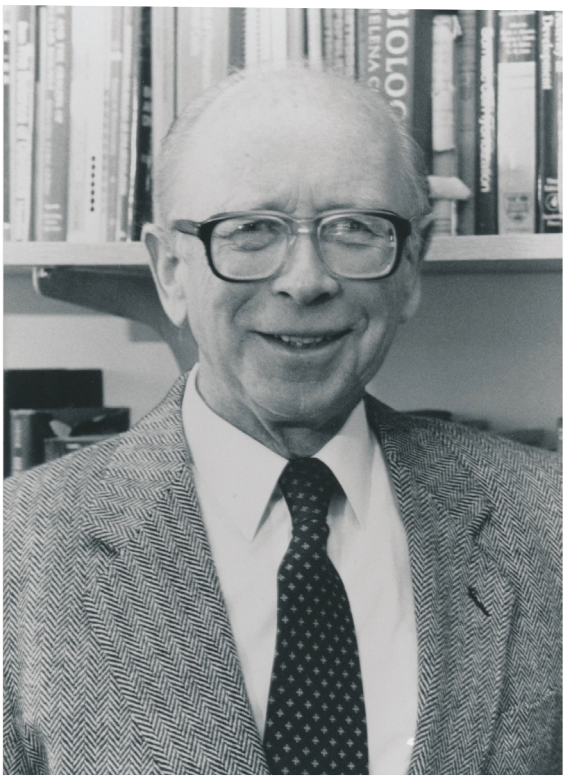
THE FACULTY OF MEDICINE
Harvard University

Arthur B. Pardee



Photograph courtesy of Ann Goodman

On February 24, 2019, one of Harvard Medical School's most distinguished and influential faculty members, Professor Arthur Pardee died. He was one of the true giants of molecular biology, whose many seminal discoveries laid the basis for our present understanding of the regulation of enzyme activities, gene expression, and cell division.

Art's scientific career began as an undergraduate studying chemistry at the University of California, Berkeley (1938-1942), where he did undergraduate research in the laboratory of Melvin Calvin, who later received the Nobel Prize for work on photosynthesis. As a graduate student at California Institute of Technology, Art worked on the chemical properties of antibodies in the lab of Linus Pauling, probably the greatest chemist of the past century. His graduate studies were interrupted by the 2nd World War, which he spent in military-related research on the toxic effects of gases and uranium. He then pursued postdoctoral studies at the University of Wisconsin in the laboratory of Van R. Potter, where he investigated energy metabolism in normal and cancer cells. The complexities of mammalian cells and the cancer problem convinced Art to focus on the simpler and more tractable metabolism of bacteria when he assumed a faculty position in the Department of Biochemistry at Berkeley in 1949. There he initially studied the effects of bacteriophage infection on bacterial metabolism and the linkages between amino acid and nucleic acid synthesis, but he went on to make several seminal discoveries about enzyme regulation.

The capstone of this phase of Pardee's work was the discovery of feedback inhibition of metabolic pathways made with his student John Gerhart. As Art noted "Living organisms usually produce their constituent molecules to meet their needs, no more or less". Through studies of pyrimidine synthesis in bacteria, they showed that when the level of the final product of this biosynthetic pathway has become sufficient for the cell's needs, the first step in the pathway is inhibited. In classic experiments, Gerhart and Pardee demonstrated that the final product of this pathway binds to the first enzyme and inhibits its further action. They further showed that the "regulatory site" where the end product binds is located at a different part of the enzyme from its catalytic site. This regulatory principle has since been extended to explain how many enzymes, pathways, and the levels of many metabolites are regulated. Elucidation of this type

of regulation was one of the most penetrating discoveries in biochemistry in the 20th century, and these studies are in most textbooks as the classic example of what is now commonly termed “allosteric regulation”.

An often overlooked, important contribution was Art’s insightful experiments in 1958 that indicated a transient intermediate between DNA and protein synthesis. This early work now is recognized by some as the initial demonstration of the discovery of messenger RNA. While Art was conducting these prescient studies, a group at the Pasteur Institute in Paris led by Jacques Monod and Francois Jacob were carrying out their classic studies showing that the bacteria adapt to growth on a new sugar, lactose, by inducing enzymes for its uptake and metabolism. In 1957-58, Art took a sabbatical at the Pasteur Institute and designed an ingenious experiment to elucidate the mechanisms for this induction, using mutant strains in which the lactose-metabolizing enzymes were either expressed continually or were silent, awaiting induction. Their elegant experiment (commonly called the PaJaMo experiment for the scientific “dream team” of Pardee, Jacob, and Monod) demonstrated that the inducible state was genetically dominant over the constitutive form, which implied that the genes for lactose metabolism are maintained in an inactive form by a repressor molecule, until it binds lactose which releases the repression. This elegant study is certainly one of the iconic experiments in molecular biology and laid the conceptual basis for many further advances in understanding gene regulation.

After 13 productive years at Berkeley, in 1961, Art with his young family moved to Princeton to head its new Department of Biochemical Sciences, to which he recruited a highly talented group of young investigators. One pioneering contribution during his Princeton years concerned mechanisms of nutrient transport and the discovery of a class of substrate-binding proteins found between the bacterial wall and cell membrane that are critical for active transport and for chemotaxis. However, Art also began to refocus his efforts to study mammalian cell growth and cancer biology. In order to better prepare themselves for research on cancer, in 1972-73, Art and the distinguished geneticist, Ruth Sager, who became Art’s second wife took a fruitful sabbatical at the Imperial Cancer Research Fund in London. Sager had done fundamental work on cytoplasmic inheritance and, like Art, decided to refocus on cancer biology, culminating in her later description of tumor suppressor genes.

Art had for some time become fascinated by how cells can “step off” from a continuous growth cycle or, more relevant to cancer, leave a quiescent state and begin to divide. During this sabbatical he formulated the notion of a “restriction point” that occurs in the G1 phase of the cell cycle, just before DNA replication, and reflects a teetering between continued growth or growth-arrest. His experiments confirmed this hypothesis and, specifically, demonstrated that if cells pass this restriction point (sometimes called “the Pardee point”), they autonomously proceed into DNA replication irrespective of what exogenous factors are present.

In 1975, Art and Ruth were both recruited to the faculty of HMS and the new Sidney Farber Cancer Center later renamed the Dana-Farber Cancer Institute, to which they brought instant eminence in basic science and were critical in helping recruit and foster the work of talented younger faculty. Art was also an active member of the Department of Pharmacology at HMS. At the Farber, Art’s work focused on the control of cell proliferation, gene expression in cancer and chemotherapy, building on his restriction point concept. He and his colleagues discovered a labile protein that controls passage or non-passage through this critical point, and went on to demonstrate that many tumor cells are deficient in this control process. In the last two decades of his long and active career, he and his colleagues focused on the actions of novel drugs for breast and other carcinomas.

One very important scientific contribution that he made in his Boston years was the development with his colleague P. Liang of a transformative method to deftly define the entire messenger RNA population of a mammalian cell, which became known as "differential display". To understand cell responses, differentiation, and disease processes, it is critically important to have a way to look at the cell's population of messenger RNAs. At the time, the methods by which the many messenger RNAs in a cell could be revealed were very laborious. "Differential display" reduced the time and cost by orders of magnitude and was widely adopted. It also allowed any messenger RNA of interest to be recovered and studied further by cloning it and determining its sequence. Although such methods have evolved further in recent years, the "differential display" method was a major technological advance at the time and remained a frontline technique for years.

For his many contribution to our understanding of biochemical regulatory mechanisms and cell growth, Pardee received many honors, including election to the National Academy of Sciences, National Academy of Medicine (formerly the Institute of Medicine), the American Academy of Arts and Sciences, and the American Philosophical Society, and numerous major awards including the Paul Lewis Award of the American Chemical Society, the Krebs Medal of the Federation of European Biochemical Societies, the Rosenstiel Medal, the 3M Award of the Federation of American Societies for Experimental Biology, the Boehringer Mannheim Molecular Bioanalytics Prize, and the Distinguished Alumni Award of California Institute of Technology. As a clear indication of his esteem and the affection of colleagues, Art was elected to the presidency of both the American Society of Biochemistry and Molecular Biology and the American Association for Cancer Research.

Beyond his major scientific achievements and many honors, Art was always remarkably approachable, gracious, soft spoken, and modest in dealing with others. He also stood out in his encouragement of young investigators and in his dedication to support this work and many of his trainees have gone on to distinguished scientific careers. After Dr. Sager's death from cancer, the last 20 years of Art's life in Cambridge and Woods Hole were shared with his wife Ann B. Goodman, who also shared his endless curiosity, broad intellectual interests, and his passion for Asian art and classical music (Art was a cellist and an avid chamber musician). He is also survived by his three sons, Michael Arthur, Richard Emil, and Thomas William Pardee, three grandchildren and six great-grandchildren. Art died in his sleep at the age of 97, and until his ninth decade, maintained an active laboratory and remained devoted to research. 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."

Respectfully submitted,

Alfred L. Goldberg, Harvard Medical School, *Chairperson*
Thoru Pederson, University of Massachusetts Medical School