Harvard Nuclear Medicine Program Fosters Clinical Decision-Making Ideas

S. James Adelstein, Preeminent Radiation Biologist, Chosen for Aebersold Award

The Paul C. Aebersold Award for Outstanding Achievement in Basic Science Applied to Nuclear Medicine will be given to S. James Adelstein, PhD, at The Society of Nuclear Medicine's (SNM) 33rd Annual Meeting this month in Washington, DC.

"Dr. Adelstein's belief that basic studies are necessary in order to establish a foundation for the future has encouraged long-term investigations that at first sight might seem tangential to nuclear medicine, but which in fact are very relevant," said Alun G. Jones, PhD, associate professor of radiology at Harvard Medical School, in his nominating letter.

As director of Harvard's Joint Program in Nuclear Medicine since it was established in 1968, Dr. Adelstein created a center devoted to clinical nuclear medicine, the teaching of residents and fellows, and research.

Four institutions (Beth Israel Hospital, Children's Hospital Medical Center, Brigham & Women's Hospital, and the Dana-Farber Cancer Institute) in Boston participate in the joint program.

As one of the first trainees in the joint program, Barbara J. McNeil, MD, PhD, witnessed its evolution into a thriving group that has produced over 700 publications in cardiovascular and oncologic nuclear medicine, radionuclide therapy, technetium chemistry, radiation biology, and clinical decision-making.

"Jim has an extraordinary ability to create centers of excellence in his division, to encourage individuals to become leaders in a given area, and to create these centers in such a way that there is appropriate collaboration throughout and synergism when possible. This multiplying effect is unusual and inspirational," said Dr. McNeil, who is professor of radiology at Brigham & Women's Hospital.

According to James W. Fletcher, MD, director of the Veterans Administration Nuclear Medicine Service, "the guidance, support, and milieu which he has generously afforded to his colleagues and students" is perhaps one of the most important aspects of Dr. Adelstein's work.

Born in New York City in 1928, Dr. Adelstein earned his BS and MS degrees at the Massachusetts Institute of Technology (MIT), his MD at Harvard Medical School in 1953, and his PhD in biophysics from MIT in 1957.

That same year Dr. Adelstein became a research fellow in medicine at Harvard, where today he is a professor of radiology. In 1968, he accepted a visiting fellowship in the Division of Nuclear Medicine at The Johns Hopkins Hospital in Baltimore and he was also appointed director of the Division of Nuclear Medicine at Peter Bent Brigham Hospital (now Brigham & Women's Hospital).

Two years later, he also became chief of Nuclear Medicine Services at Children's Hospital Medical Center. In addition to directing these clinical and research departments, Dr. Adelstein has been dean for Academic Programs at Harvard Medical School since 1978.

Dr. Adelstein's contributions to radiation biology fall into three distinct areas: the effects of radiation on the synthesis of deoxyribonucleic acid (DNA), and on the incorporation of pyrimidine nucleoside precursors into DNA; the radiation chemistry of enzyme proteins and chromatin; and the biologic effects of radionuclides incorporated into cellular DNA.

S. James Adelstein, MD, PhD

Radiation-Resistant Pathways

In Dr. Adelstein's early work, he observed that radiation doses that markedly inhibit the utilization of some nucleosides do not affect the main pathway leading to nucleotide synthesis (*1*). This process, unlike the steps leading to DNA synthesis, is relatively radiation-resistant.

"These studies were important in demonstrating that many factors can influence the rate of incorporation of exogenous thymidine into DNA.

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Therefore, the quantitative uptake of thymidine as a direct measure of the rate of DNA synthesis must be employed with great caution," explained Dr. Adelstein.

His work in radiation chemistry extends over a 20-year span. In the early 1960s, he studied the radiolysis of proteins, such as diphosphopyridine nucleotide (DPN)-pyrophosphorylase and ribonuclease, and found and identified the limited spectrum of radiolysis products responsible for enzyme inactivation (*2,3*).

In addition, Dr. Adelstein delineated the contributions of specific, primary aqueous radicals to the changes in the activity, conformation, and amino-acid composition of certain enzymes (*4,5*).

Scavenging Aqueous Radicals

"Other work provided experimental support for the concept that cellular components provide considerable protection for its enzymatic constituents against the effects of radiation, either by scavenging aqueous radicals or by close association with the enzyme molecules themselves," he explained (*6*).

Focusing his attention on the effects of radiation on chromatin, Dr. Adelstein's group found that DNA is much more sensitive to induced single-strand breaks when it is irradiated in isolated chromatin than when it is irradiated in whole cells prior to chromatin isolation. He also found that DNA in isolated chromatin is less sensitive to radiation than naked DNA (*7*).

Mechanisms of Protection

"These findings suggest that aqueous radicals contribute significantly, albeit indirectly, to the radiation damage of DNA in isolated chromatin," said Dr. Adelstein, "and again yields evidence that intact cells provide mechanisms for the protection of such critical molecules."

The research group also showed that the hydroxyl radical is the most efficient for inducing nucleoprotein-DNA crosslinks in chromatin (when isolated as well as when irradiated as part of intact cells), and Dr. Adelstein made the significant observation that core histones predominate in forming such crosslinks in irradiated chromatin (*8,9*).

Aüger-Emitting Radionuclides

"Jim Adelstein's published work on Aüger emitters (*10–13*) are major papers in the understanding of the biologic effects of these radionuclides, and I believe that this work forms the rational background for the development of therapeutic radiopharmaceuticals," said Michael J. Welch, PhD, professor of radiation chemistry at the Mallinckrodt Institute of Radiology in St. Louis.

Aüger-emitters generate highly localized energy discharges, yielding up to 100 eV within a 10-angstrom sphere around the site of decay in DNA, explained Dr. Adelstein. "Incorporated into DNA, these radionuclides are highly toxic, whereas their cytoplasmic location contributes only minimally to radiation-induced cytotoxicity," he added.

Elusive Goal of Therapy

Dr. Adelstein and his colleagues have also shown that Aüger-emitters such as iodine-125 "are extremely efficient inducers of malignant transformation *in vitro*—even at doses low enough to avoid measurable cell killing (*14*). While the transforming effects of Aüger-emitting radionuclides render them a hazard to normal cells, their locations to a malignant tumor might provide a very potent therapeutic modality," he noted.

Although easily conceptualized, the successful targeting of radionuclides to tumor cells and the subsequent deposition of lethal amounts of ionizing radiation remain elusive goals, warned Dr. Adelstein. "Simply stated, the difficulty lies in the scarcity of specific carrier molecules and radionuclides with appropriate decay characteristics," he said.

To discover the desired therapeutic activity and distributions, Dr. Adelstein has explored several biologic systems with various radionuclides and carriers: iodine-125 iododeoxyuridine (IUdR), a thymidine analogue, in experimental malignant ascites; iodine-125 iodotamoxifen, an antiestrogen, in cultured breast cancer cells; and alpha-emitters in colloid therapy (*15,16*).

"This work has led quite logically to one of the first serious evaluations of radionuclide microdosimetry," said B. Leonard Holman, MD, director of Clinical Nuclear Medicine at Brigham & Women's Hospital.

Ideas Ahead of Their Time

Dr. Holman said that he believes Dr. Adelstein has not received the recognition he warrants partly because "he frequently works on ideas that are well ahead of their time." For example, the full clinical implications of Dr. Adelstein's collaborative work on target-specific tracers for tumor therapy, dating back to 1975, have only recently been realized, noted Dr. Holman.

"Dr. Adelstein was also years ahead

Past Recipients of the Paul C. Aebersold Award

1973	William G. Myers, PhD, MD
1974	Paul V. Harper, MD
1975	Gordon L. Brownell, PhD
1976	Michel M. Ter-Pogossian, PhD
1977	Powell Richards
1978	William H. Oldendorf, MD
1979	John McAfee, MD
1980	Michael J. Welch, PhD
1981	Alfred P. Wolf, PhD
1982	Gopal Subramanian, PhD
1983	Michael E. Phelps, PhD
1984	John S. Laughlin, PhD
1985	John H. Hubbell, MS

of his contemporaries in the area of clinical decision-making," said Dr. Holman. "As early as 1970, Adelstein *et al.* described the methodology for evaluating new diagnostic tests," he added (*17*).

As Dr. McNeil recalled, Dr. Adelstein urged her to "dust off my math books and analytic skills gained as a graduate student, and to apply them to a new, relatively underdeveloped field—medical decision-making."

He further elaborated on a comprehensive approach to formalize the way that information from nuclear medicine and radiologic procedures can be quantified and presented, and to identify the important factors in understanding the impact of new technologies (*18–20*).

According to Dr. McNeil, Dr. Adelstein helped crystallize a general approach to technology in medicine by enumerating four areas that needed evaluation: the relationship between technologic improvements and diagnostic accuracy; the relationship between databases, accuracy, and predictive values; the potential for using receiving operator characteristic (ROC) curves; and the relationship between diagnosis and health outcome.

Recognizing some of the early biases in data collection, "he cautioned us and others about the heterogeneity of populations having the diagnostic examination versus the population having independent proof of disease state," explained Dr. McNeil.

Validating Clinical Algorithms

He further recognized that this heterogeneity might have an impact on the evaluation of thyroid function tests, and early on realized the importance of validating clinical algorithms.

"He was actually quite prescient in emphasizing this validation point because it had not been emphasized in the popular medical literature until the early 1980s," added Dr. McNeil.

As an example of his broad outlook, Dr. McNeil related how Dr. Adelstein handled a request from the World Health Organization (WHO) and the International Atomic Energy Agency (IAEA) to study nuclear medicine resources in developing countries. He encouraged his group to understand not only how resource allocation decisions would affect patient care, but also how they would affect research and teaching in the context of the region's health priorities.

Macroscopic Societal Concerns

Dr. Adelstein has the unusual ability to see past microscopic concerns to macroscopic societal concerns, she added.

The award commemorates the scientific accomplishments of the American physicist Paul C. Aebersold, PhD (1910–1967), the first director of the Division of Isotopes Development at the Atomic Energy Commission.

Dr. Adelstein has been a member of the SNM since 1968, and was active on many committees in the 1970s. Today, he is a member of the newly reorganized ad hoc Radiation Effects Committee, which will report new developments in health effects of low, medium, and high levels of ionizing radiation.

Linda E. Ketchum

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