Henry N. Wagner, Jr., MD

Nuclear Medicine: 100 Years in the Making

The field of nuclear medicine marks its 100th Anniversary this year. Henry N. Wagner, Jr., MD, a professor of medicine, radiology and environmental health sciences at Johns Hopkins Medical Institutions in Baltimore, MD, highlights the most important advances of the century. This commentary is based on the Centennial Lecture which he presented during the Plenary Session at the 1996 SNM Annual Meeting in Denver, CO.

One hundred years ago, Henri Becquerel started the sequence of events that produced perhaps the greatest scientific truth of all time, that is, the discovery that mass is condensed energy. He also taught us that if you find something unexpected and explore it further, it could become the greatest discovery of your life and end up making you famous.

Nuclear medicine began with physics, expanded into chemistry and instrumentation, and then greatly influenced various fields of medicine, such as endocrinology, cardiology and the neurosciences. Today, nuclear medicine clearly is becoming involved in oncology and genetics. In the development of nuclear medicine, each link in the chain of events led to the subsequent link. The chain is still expanding into new fields of medicine.

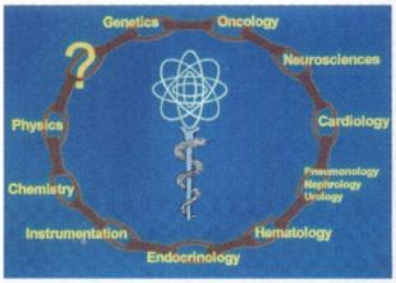
In 1903 when Marie Curie won the Nobel Prize in physics, she brought more honor to the Nobel Prize than the Nobel Prize brought to her. She was world famous, and the Nobel Prize was so new that no one had heard about it. There was a great argument at that time between the physicists and chemists— each of whom wanted to give Madame Curie the prize in their particular field—but the physicists won out. She later won the Nobel Prize in chemisty in 1911.

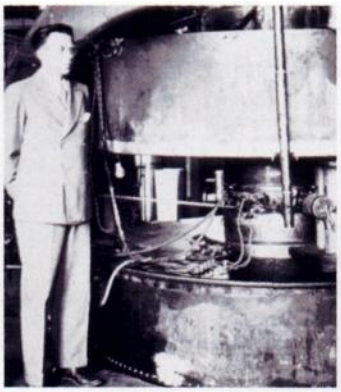
The Discovery of Artifical Radioactivity

Marie's daughter, Irène, joined her in the Radium Institute where she met and married Frédérick Joliot. In 1934, they showed that radioactive decay did not occur only in naturally-occurring elements, but with the bombardment of aluminum with the emissions of polonium, the element that her mother had discovered, they were able to induce artificial radioactivity. The first radioactive tracer produced artificially was a positron-emitting isotope of phosphorus.

Frédérick Joliot was one of the group of physicists who explained what Becquerel had observed and what Marie Curie had isolated in her discovery of polonium and radium. Working with Ernest Rutherford, Joliot convinced the world of the transmutation of elements and the fact that radiation was coming from inside the atom itself, and not from some external force.

The invention of the tracer principle by Georg de Hevesy in 1912 illustrates the evolution of radiation research from the domain of physics to chemistry, and then in 1923 into the study of biochemistry. He was the first to elucidate what is perhaps the other important principle in biology—the principle of





Photos top left clockwise:

Oncology and genetics are the newest links in the developmental chain of Nuclear Medicine; other developments are certain to follow. ➔ Marie Curie and her daughter Irène in their laboratory at the Radium Institute in Paris. ➔ Ernest O. Lawrence with the fourth version of the cyclotron he invented. For this achievement he was awarded the Nobel Prize in physics in1939. ➔ Georg de Hevesy was the first to demonstrate the principle of the dynamic state of body constituents, a fundamental concept in biology and the foundation on which nuclear medicine is built. ➔ Benedict Cassen assessing data from the rectilinear scanner he invented in 1950. ➔ Hal O. Anger in 1958 with the scintillation camera he invented.

the dynamic state of body constituents. His first experiments showed how lead moved from the soil, through the body and then back into the soil.

The first use of radioactive tracers for diagnosis was performed at Harvard in 1925 by Herman Blumgart. He injected solutions of radon in one arm vein and then measured how long it took to reach the other arm, calling the measurement the velocity of the circulation. Two years before, Ernest Lawrence began work on his cyclotron. The field of nuclear medicine is known for its use of radioactive tracers to measure in vivo biochemistry in experimental animals and in living human beings. One of the very earliest brain studies was performed in 1948, by George Moore, MD, a neurosurgeon at the University of Minnesota, using di-iodofluorescein to localize brain tumors at surgery.

Today nuclear medicine is returning to the operating room. New devices include a beta detector system being developed at UCLA. At the University of Tokyo, surgeons used a combination of ^{11}C-methionine and measurements of regional blood flow to delineate the exact areas of the brain to be removed at surgery.

About the same time that Watson and Crick described the structure of DNA, Benedict Cassen and his colleagues at UCLA invented the rectilinear scanner based on the use of scintillation detectors rather than Geiger-Mueller tubes. My own introduction to nuclear medicine was in 1957 at Hammersmith Hospital in London where one of my chores, in addition to working in the cyclotron facility, was point counting over the neck with a hand-held radiation detector after injection of radioiodine to determine whether a thyroid nodule was "hot" or "cold", that is, it did or did not accumulate radioiodine.

In 1958 at the Society of Nuclear Medicine meeting, Hal Anger presented his first scintillation camera. What made the scintillation camera so valuable was ^{99m}Tc. Paul Harper and Catherine Lathrop realized the wonderful physical characteristics of ^{99m}Tc and began to produce a whole series of useful compounds. The scintillation camera made it possible to perform dynamic studies which led to nuclear cardiology.

The first tracer used to examine myocardial perfusion was ^{43}K. It resulted in very poor images; so we stopped the motion of the heart by electrocardiographic "gating" of the scintillation camera. As it turned out, Dr. Bert Pitt looked at images obtained at end-systole and end-diastole to stop the motion of the heart and told us that observing, not just stopping, the motion of the heart would make it possible to image ventricular wall motion.

Investigators at the National Institutes of Health divided the cardiac cycle into 16 time frames instead of just end-systole and end-diastole, making ventriculography what it is today.

David Kuhl invented tomography in the early 1960s. He performed the first [^{18}F]FDG studies on his Marc IV positron-emitting tomograph. Michael Phelps, Michel Ter-Pogossian, Edward Hoffman and their colleagues then worked on further development of PET. Ter-Pogossian had been stressing the use of positron-emitting tracers, specifically ^{15}O, for years, beginning in the 1950s.

Quantification in Nuclear Medicine

In 1963, nuclear medicine expanded into pulmonology when the first lung scan was performed in a patient with massive pulmonary embolism. The use of lung scanning in the urokinase pulmonary embolism trial—the first multi-institutional, large-scale study of its kind supported by the National Institutes of Health—led to quantification in nuclear medicine by computers.

Both PET and SPECT have advanced together since 1982. Both are essential for the further development of the field. Nothing, perhaps, has brought them more closely together than the use of dual-headed cameras operating in the coincidence mode or so-called "SPECT scanning" using tracers such as FDG.

It is my belief that eventually all nuclear imaging will be multi-energy, neither dedicated to PET nor SPECT. Why? Since there is a role for positron-emitting tracers and single-photon-emitting tracers, we will want to perform multiple studies with multiple tracers at the same time in the same patient without the patient moving, which would happen if the studies were conducted separately. Double or even triple radionuclide studies would be based on using the 511-keV positron emission, and the others using single-photon emissions.

Neurology and Oncology: Newest Links in Chain

Almost 50 years ago, Otto Loewi discovered chemical neurotransmission which earned him the Nobel Prize. Later, in studies of a monkey Louis Sokoloff showed that closing one of the monkey's eyes resulted in decreased glucose utilization in the cerebral cortex. Clearly one of the practical applications of Sokoloff's, Wolfe's and Kuhl's studies with FDG was the discovery that many tumors are characterized by the avid accumulation of glucose— a major new advance in nuclear medicine.

The first imaging of positron-emitting tracers that bind to neuroreceptors in the brain was performed at Johns Hopkins Medical Institutions in Baltimore. Similar studies with single-photon-emission tracers were performed by Eckelman, Reba and their colleagues at George Washington University. It's almost unbelievable that 10% of the over 1200 papers presented at the 1996 SNM Annual Meeting involved neurotransmission.

Oncology, too, is clearly at the top of the chain of progress that I referred to earlier. I mentioned how one field leads to another: lungs into heart, heart into brain. One case in point is a recent study in which researchers used a tracer targeting dopamine receptors in the brain to study dopamine receptors in pituitary tumors. Another example can be found in the work of Jean Claude Reubi of the University of Berne, Switzerland, who extensively studied the receptors in tumors removed at surgery. Many tumors express a high incidence of somatostatin receptors, vasoactive intestinal peptide receptors, cholecystokinin receptors and substance P receptors, all of which can serve as tumor markers. In terms of treatment benefits, identifying somatostatin receptors on a tumor means patients can be treated with nonradioactive somatostatin and their chances of survival are much better than with conventional chemotherapy. Thus, we see diagnosis and treatment by chemistry. Tumors can also be treated by high doses of radioactive receptor-binding tracers.

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100 Years *(Continued from page 24N)*

No commentary on the history of nuclear medicine would be complete without at least mentioning another partnership couple: Solomon Berson and Rosalyn Yalow. Just as we had Marie and Pierre Curie, Frédérick and Irène Joliot, we also owe a great debt to Berson and Yalow. The most recent Nobel Prize awarded in the field of nuclear medicine was to Dr. Rosalyn Yalow in 1977.

Over the last 100 years, nuclear medicine has expanded to encompass molecular nuclear medicine, in vivo chemistry and physiology, based on a foundation that includes, more recently, its sister sciences, genetics and pharmacology. When I was in medical school, the practice of medicine could be thought of as using the history and physical based on an infrastructure of pathological anatomy. As a result of the work of Hevesy, Schoenheimer, Rittenberg and many others, we now add the principle of molecular homeostasis, which can be measured by nuclear medicine techniques, to the history and physical. We also add genetic pathology to pathological anatomy.

In the past, I have referred to nuclear medicine as being the bridge between molecular biology and genetics and clinical practice. In honor of the nuclear medicine pioneers of yesterday, I would like to quote a poem called "The Bridge Builders":

Some old men going down a lone highway came at evening cold and gray to a chasm vast and deep and wide, and built a bridge to span the tide.

"Old men," said a fellow pilgrim near, "you are wasting your strength in building here. You never again will pass this way. Why do you build this bridge today?"

The men replied, "There followeth us youth whose feet this way must pass. The new builders are fellow men. We are building this bridge for them."

— Henry N. Wagner, Jr. MD

PROPOSED BYLAWS CHANGE NOTIFICATION

The Subcommission on Bylaws has received notice of and reviewed the following proposed amendments to the SNM Bylaws. As required by our Bylaws, notice of these proposals will be communicated to the membership at least 60 days prior to the next meeting of the House of Delegates. The subcommission understands that this communication will be via publication in SNM *Newsline* in *The Journal of Nuclear Medicine*. The delegates will then discuss and vote on the amendments at the 1997 Mid-Winter meeting of the House of Delegates in Palm Springs, CA.

The Bylaws additions are indicated in **bold** typeface and deletions are *italicized* in brackets.

1. Add a new Commission of the House of Delegates to have overall responsibility for issues related to Radiopharmaceuticals (submitted by the Board of Directors):

   Article XII Commissions and Committees
   Section 1: Description
   Commission on Radiopharmaceuticals

2. Consolidate the Commission on Practice with the Commission on Health Care Policy (submitted by the Board of Directors):

   Article XII Commissions and Committees
   Section 1: Description
   [(6) Commission on Practice]
   (7) Commission on Health Care Policy **and Practice**

3. Rename Subcommissions to Committees (submitted by the Bylaws Committee):
   Article XII Commissions and Committees
   Section 1: Description
   A. The House of Delegates shall have the following Standing Commissions, as well as [*Subcommissions]* **Committees organized under the Commissions** and established as circumstances warrant....

4. Revise the method for determining the number of delegates for each Council by removing the requirement that only "primary" Council members be counted in determining the Council membership used to calculate the number of delegates (submitted by the Board of Directors):

   Article VII House of Delegates
   Section 3: Composition
   A.(5)....
   [Individuals joining more than one (1) Council shall declare one (1) Council as primary and, for determining the number of Council Delegates, shall be counted only on the Council of primary choice.]