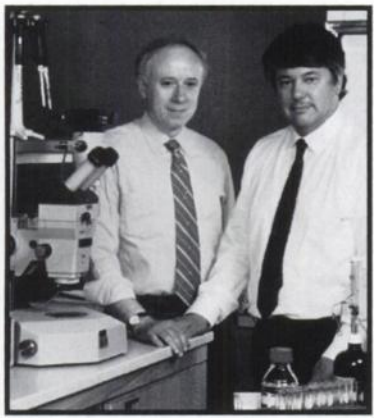
Nobel Laureates Foretell Future Based on Past Achievements



Nobel prize winners who used radionuclides in their research (from top, clockwise): Alfred Gilman, MD, PhD, for his discovery of G-proteins; Joseph Goldstein, MD, and Michael S. Brown, MD, for their discovery of the LDL receptor; Rosalyn S. Yallow, PhD, for her invention of radioimmunoassay; Martin Rodbell, MD, for his work on intercellular communications.

When Rosalyn S. Yalow and Solomon A. Berson began researching adult-onset diabetes in the late 1950s, they never suspected their metabolism studies using ^{131}I-labeled insulin would spur the development of a host of new technologies. Berson and Yalow observed that the radioactive insulin cleared from the pancreas more slowly in diabetic patients. They speculated that the slower clearance was caused by the binding of radiolabeled insulin to antibodies made by a diabetic patient's body in response to synthetic insulin treatments. They found, however, that this theory was impossible to prove because the immunological technology available at that time was not capable of detecting the tiny antibodies to which insulin binds. Berson's and Yalow's need for a technology to measure the smallest biological substances in the body resulted in their development of radioimmunoassay, a technique which has had a tremendous influence on the way physicians practice modern medicine.

For the past four decades, a vast number of Nobel prize winners in medicine have relied on radionuclides for their discoveries, and they are now seeing their research applied in ways that they never envisioned. Berson's and Yalow's radioimmunoassay technique has revolutionized researchers' abilities to measure virtually all biologic substances and opened up new doors to help diagnose and treat such diseases as prostate and ovarian cancers. Other laureates have used radionuclides to study the fundamentals of neuropeptides, cellular communication mechanisms and cholesterol receptors, which they foresee will further the understanding of cancer and heart disease. Given the advances made so far, *Newsline* called on several Nobel laureates to discuss their groundbreaking research with radionuclides, to predict the significance of their findings on further research and to speculate on the role nuclear medicine imaging will play in future advances.

The Technique that Spawned a New Era in Medicine

Radioimmunoassay measures concentrations of an unknown substance by comparing the ratio of the substance's ability to disrupt antigen binding to the already known disruptive actions of specific antibodies. Measurements are obtained by the use of radionuclides such as ^{131}I and ^{60}Co which facilitate the reaction of a radioactive antigen with a specific antibody. Radioimmunoassay has become a useful prospective device to evaluate protein and enzyme binding to cells and to gauge the effectiveness of various tracers in combating a wide variety of diseases. It has become the gold standard for screening blood donations for hepatitis and has led to the development of screening tests for prostate and ovarian cancers. Moreover, its ability to compare substances that bind to antibodies has led to widespread understanding about the interrelationships between hormones in the body and the mechanisms which enable them to be released throughout the body to combat foreign invaders.

Trained as a physicist at the University of Illinois, Yalow received the Nobel prize for Physiology or Medicine in 1977 alone because Berson, her friend and colleague of more than 20 years, died 4 years earlier. In acknowledging Yalow's work, the Nobel committee stated that radioimmunoassay represented "an enormous development in hitherto closed areas of research." Her colleagues agreed the technique could provide the building blocks for exploring the workings of each hormone in the body. In fact, it contributed significantly to the work of Roger C. Guillemin, MD, PhD and Andrew V.

Schally, PhD—who shared the prize with Yalow in 1977—for their discovery that the neuropeptide somatostatin inhibited the release of the growth hormone somatotropin in brain tumors. Guillemin and Schally used radioimmunoassay to identify and synthesize three brain hormones that are used by the hypothalamus to regulate the release of pituitary hormones which help curb the growth of malignant lesions. Since 1978, Schally's research has been focused almost exclusively on developing hormonal treatments for prostate, ovarian, breast and brain cancers. In his recent work on brain cancer, he used the somatostatin analogs ^{121}Rc, ^{90}Rc and ^{161}Rc which can cross the blood-brain barrier and shrink brain malignancies that have highly expressed somatostatin receptors.

Yalow envisions that radioimmunoassay will continue to shed new light on the minute workings of the human body: "We began using radiolabeled materials in our studies, and the research of the future is going to continue to utilize the enzyme labels that researchers are employing now. This means that all the hormones and other chemical substances in the body will eventually be studied and understood." While Schally declined to speculate on the future, he acknowledges that his and Guillemin's discoveries have resulted in an explosion of hormonal therapies "geared towards treating cancer patients without the harmful side effects of chemotherapy."

The Future of Cellular Communication

A man who has spent the majority of his research career at the National Institutes of Health Science in Research Triangle Park, North Carolina, Martin Rodbell, MD— co-winner of the 1994 prize for Physiology or Medicine — did pioneering work on cellular communication mechanisms. This led to the discovery of G-proteins by Alfred Gilman, MD, PhD, at the University of Texas Southwestern Medical Center in Dallas who shared the prize with Rodbell. Rodbell's work postulated that G-proteins attach to receptors on the surface of a cell and relay information about the functions of neighboring cells.

Rodbell speculated that the G-proteins occurred in the form of multimers (such as actin), which are part of the cytoskeleton of the cell. With the help of PET nuclear imaging devices, Rodbell and his associates have been able to peer at the structure of the cytoskeletal network. They used radionuclides to compare the ability of certain hormones to enhance cellular communication, and these comparisons led to the discovery that cell receptors are not as passive as they appear. Rodbell and others have found that when receptors are activated by radionuclides they are able to bind to hormones and then actually penetrate the cell membranes to communicate information. Rodbell's discoveries have also revealed that receptors are selective in the proteins that they receive and can even alter the way they receive certain proteins. "The cytoskeletal network," said Rodbell, "is a big part of the weblike cellular communications systems of the cell. The cytoskeleton works like a complicated subway grid: the vesicles ride along a complex circuitry of rails which help determine the health and functioning of the cell. A change in the circuitry of the subway route means that there is a change in the ability of the cell to ward off disease in the future." A breakdown in com-

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Nuclear Medicine Stands on the Shoulders of Giants

The following Nobel laureates made discoveries that laid the foundation for nuclear medicine as it is applied today.

1901-**P** . . . Wilhelm Röntgen	1935-**P** . . . James Chadwick
1903-**P** . . . Henri Becquerel	1936-**P** . . . Carl Anderson
Pierre Curie	1938-**P** . . . Enrico Fermi
Marie Curie	1939-**P** . . . Ernest Lawrence
1906-**P** . . . Joseph Thomson	1943-**C** . . . Georg C. de Hevesy
1908-**C** . . . Sir Ernest Rutherford	1944-**C** . . . Otto Hahn
1911-**C** . . . Marie S. Curie	1946-**M** . . . Hermann Muller
1918-**P** . . . Max Planck	1951-**C** . . . Glenn T. Seaborg
1921-**C** . . . Frederick Soddy	Edwin McMillan
1921-**P** . . . Albert Einstein	1956-**P** . . . John Bardeen
1922-**P** . . . Niels Bohr	Walter Brattain
1924-**M** . . . William Einthoven	William Shockley
1927-**P** . . . Arthur Comptom	1959-**P** . . . Emilio Segre
Charles Wilson	1961-**P** . . . Robert Hofstadter
1934-**C** . . . Harold C. Urey	1968-**P** . . . Luis Alvarez
1935-**C** . . . Frederic Joliot	1977-**M** . . . Rosalyn S. Yalow
Irene Joliot-Curie	Roger Guillemin
	Andrew Schally

P = Physics; **C** = Chemistry; **M** = Medicine.

*Reprinted from the historical documents of William G. Myers housed in the SNM Archives in Reston, VA.

Radiopharmaceutical Approval

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Europe. The product can be advertised in medical journals and sold to physicians and hospitals; what's more, it is usually covered by health insurance.

In comparing the approval process for OctreoScan in Europe versus the U.S., Doedens said there was little difference in terms of the reviewer's questions and the approval time (19 months in the U.S. versus 14 months in Holland). "The major difference," he said, "is that it was possible to get preapproval sales in Europe, which is not allowed in the U.S." Doedens said advanced sales of OctreoScan were a significant impetus for boosting sales once the product was approved. Even though the synthetic peptide was approved around the same time in both Europe and the U.S., its sales in this country are still lagging behind its sales abroad.

The Somewhat Disjointed European Union

In 1992, the drug approval process became centralized for members of the European Union (which includes the Western European countries such as Great Britain, France and Germany). Radiopharmaceutical manufacturers still apply to a specific country for approval—for instance Holland handles most of the NDA's for monoclonal antibodies—but the Union coordinates the approval for the rest of its member countries. Although the European Union was founded on the best intentions, "it is becoming more like the FDA with its bureaucracies and regulations," said Doedens. Once a new drug is approved by one country, the other members have an opportunity to comment on the application when it reaches the Union, which can slow down the process. What's more, the Union has set up more restrictive rules for promoting a product before it is approved.

Perhaps the largest problem has centered around trying to get 16 countries to agree to one set of regulatory laws. Some countries have traditionally taken a much tougher stance on regulating imaging agents than others. Holland and Finland, for instance, had never regulated radiopharmaceuticals as drugs before they joined the Union. Great Britain had very strict regulatory laws, and Germany went as far as to regulate PET radiopharmaceuticals, which the FDA is now considering.

For the future, the FDA is currently looking into an worldwide cooperation of sorts. It is participating in an international conference on harmonization next month in which agency representatives will meet with Asian and European drug regulatory officials, as well as technical experts in the pharmaceutical industry, to see if they can establish some common guidelines for fast-tracking drugs that have already been approved in other countries. In the meantime, products like Myoview must still go through separate review processes in order to be distributed in Europe, Japan and the U.S.

This past April, the fate of Myoview was seen as uncertain when the FDA safety officer called and said her department was still "waffling" on whether to write an approvable letter. In the meantime, Amersham executives were told they needed to answer the chemistry reviewer's questions on a degradation study and they also needed to revise Myoview's package insert.

Things started looking up in May, when Waterman and other Amersham executives received word from the FDA safety officer that an approval letter was in the works—although the letter still needed review by at least a dozen FDA officials before it could be sent. On July 14, 1995, Amersham received an official "Approvable" letter from the FDA accompanied by 10 pages of questions and a request that an additional "Phase IV" clinical study be performed after approval. On August 22, Amersham executives mailed off their response to the FDA's questions. It was more than 10,800 pages long. As of press time, Myoview still had not received official FDA approval. There will probably be a few more rounds of letters with questions and requests before the process is finished. Watterman says they're hoping for approval by the end of this year—two years after the FDA's original deadline. When Myoview will actually be approved is still anyone's guess.

Deborah Kotz

Nobel Laureates

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munications, he said, can allow cells to multiply wildly or disease-causing pathogens to run rampant.

Although formally retired, Rodbell continues to do research on cellular communications and has firm views on where he thinks the field is heading. "Future research will continue to focus on assessing cellular communications to show how the communications networks in similar cells are in fact very different," he said. For instance, cloned cells have been found to have different internal structures and communication networks. "We think, and hope, that people are going to follow our lead, and with the benefit of ever-improving imaging technologies, such as PET, gain better and better glimpses of the functioning of the intercellular communications grid," said Rodbell. Gilman, who currently serves as the Raymond Willie Distinguished Chair in Molecular Neuropharmacology at the University of Texas Southwestern Medical Center, is even more optimistic: "We anticipate knowing every molecule involved in G protein-mediated transmembrane signaling—all of the hundreds of receptors, G proteins and effectors. We will thus be able to decipher the complete wiring diagram for the signaling switchboard for every cell. This knowledge will have enormous implications for drug development and the rational treatment of disease."

A New Understanding of Cholesterol

Using radionuclides for their research on cellular receptors, Michael S. Brown, MD and Joseph Goldstein, MD, from the Molecular Genetics section at the University of Texas, shared the 1985 Nobel prize for their discovery of a low-density lipoprotein receptor (LDLR) and its role in familial hypercholesterolemia. "While knowledge of receptors surfaced almost 50 years ago when investigators tried to con-

ceptualize substances' interaction with cells and subsequent cellular reactions to the substances, it has only been in the past 15 years that specific radiopharmaceuticals have been developed to interact with receptors," said H. William Strauss, MD, of the division of nuclear medicine at Stanford University School of Medicine.

Brown and Goldstein specifically used radionuclides such as ^{125}I to detect defects or inadequacies on LDL receptors which can cause an excessive increase in blood cholesterol levels leading to premature arteriosclerosis. The receptors work by stimulating transcription, which enables the cell to control levels of plasma cholesterol circulating throughout the body. Brown and Goldstein found that the LDL receptor is a transmembrane protein in the cell that mediates the uptake and the degradation of plasma cholesterol through tiny sacs located in the cells called lysosomes. Experts in the field say Brown's and Goldstein's discovery represents an enormous development in furthering the understanding of hypercholesterolemia. It also sheds insight on why cholesterol levels vary among individuals independent of their diets.

In an interview with *The New York Times*, Goldstein observed that future research will point "to the importance of this receptor in the control of blood cholesterol and how the receptor can be raised through drugs and a low cholesterol diet." John M. Dietzschy, MD, who has also researched LDL receptors, said future advances will enable scientists to "tell a drug company how to design new medical treatments. In the next 10 years, we'll be able to develop and test medicines to improve the receptors and lower cholesterol levels in humans."

Regardless of whether these Nobel laureates are the beneficiaries of past research or the visionaries of future advances, or both, their discoveries will inevitably have a lasting impact on the practice of modern medicine. Where, for example, would nuclear medicine be at the present time without the radioisotopes that Glenn T. Seaborg and John J. Livingood—themselves Nobel laureates—discovered in the late 1930s and early 1940s at Berkeley? "Our motivation in searching for new radioisotopes was simply the fascination of exploring an exciting new frontier of science," said Seaborg in a recent *Journal of the American Medical Association* article. Echoing the sentiments of other Nobel laureates, he said, "we very often cannot predict the practical applications of basic science discoveries, but we can predict that some applications will occur later to the enduring benefit of mankind."

Brendan M. Peter

Clarification

The September *Newsline* article titled, "Investigating Chernobyl-Induced Thyroid Cancer: Politics vs. Science" discussed some of the efforts to study persons exposed to radiation from the Chernobyl nuclear power plant accident and suggested that the effectiveness of the studies was compromised because of personal or national reluctance to cooperate with other participants. These efforts could be facilitated by increased communication among the various participants in the several projects underway in Belarus, Russia and the Ukraine. The comments were not intended to be critical of the several projects or to suggest that difficulties were impeding the progress of participating organizations. The number of private, national and international organizations that seek to assist those who have suffered because of this accident is large and includes the World Health Organization, the European Union, Japan, Germany, Italy, France, Finland, Canada, The Netherlands, the United States (including studies supported jointly by the Department of Energy, the Nuclear Regulatory Commission and the National Cancer Institute, plus assistance provided by the Agency for International Development) and other countries, a number of which, including the United States, have bilateral agreements with one or more of the former Soviet republics.

Formal and informal communications and meetings between and among these participants have led to mutual understandings and consensus on many of the scientific and programmatic issues involved in an effort to avoid overlap and duplication of projects, personnel and patients, and to maximize resources. Multinational cooperation always is a challenge, but the benefits to be derived from these studies outweigh any of the difficulties noted in the September *Newsline* article. I commend the efforts of the various groups to obtain needed scientific data and to provide support for the children of Chernobyl. It is my hope that this additional perspective will add balance to the impressions previously presented.

—Conrad Nagle, MD,
Editor, Newsline