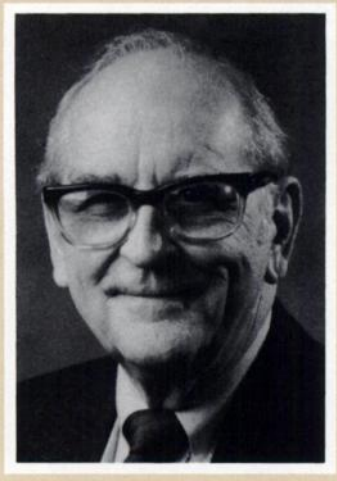
PEOPLE IN NUCLEAR MEDICINE



Frederick J. Bonte, MD

AS EARLY AS 1946, THE U.S. Army saw the need for what it called "nuclear attack survival officers." Before World War II ended, a 26-year-old Army Air Corps captain named Frederick J. Bonte, fresh out of medical school, was assigned to nuclear survival duty and found the indoctrination–technical manuals detailing the uses and effects of radiation–intriguing enough to pursue a fellowship in radiation biology after the war. He quickly rose through the ranks of academic medicine to become chairman of radiology at the University of Texas Southwestern Medical Center in 1956. Dr. Bonte ultimately accepted an administrative post and became dean of Southwestern Medical School in 1973. Eight years later he stepped down, not to retire, but to resume again a very active research career as first director of Southwestern's Nuclear Medicine Center, a free-standing research laboratory that he still directs.

Newsline: Why did the idea of using radiation in medicine hold such powerful fascination in the 1940s?

Fred Bonte: I became fascinated with how you could use this modality in several ways. If you passed radiation through the human body and allowed it to be differentially absorbed you could make shadows on photographic films that would allow you to make diagnoses that couldn't be made any other way–it completely altered the course of medicine. I then learned that physicians were using much larger doses of these same photons, directed in an intelligent way, to destroy tumors that were not amenable to any other treatment. You could destroy it and on some occasions you could cure it. I found that fascinating.

Newsline: How did nuclear medicine fit in?

Fred Bonte: What was to become nuclear medicine was developing as a part of radiation therapy. To think of giving an isotope of a common element that would preferentially locate in something like a thyroid tumor, evoked the vision of whole families of drugs of this sort containing radioactive principles. My chief at Western Reserve University in 1948, Hymer Friedell, was a radiologist who had been the chief of health physics at Oak Ridge during the war. He kept telling me that within a decade, cancer will be a thing of the past, that there will absolutely be whole families of radioactive drugs that will be selectively taken up by tumors and extirpate them. A challenging idea, but he was wrong.

Newsline: Jumping back into research after eight years as dean of a medical school must have been tough.

Fred Bonte: It was a hell of a wrench. I went over to the lab the first morning and a young guy who I'd hired as a medical student to run our primitive computer was now running the show as chief of nuclear medicine. I used to stand in the back row while the new generation and the house staff read the films until little recognition patterns began to light up in my brain. I learned new tests that had come about while I was gone. I kept trying to read all the time I was dean but there's a difference between reading about it and actually doing it in medical practice. It took me the better part of three years to get my eye back, to be able to recognize abnormal patterns easily and to associate them with the right diagnosis.

Newsline: How did you focus your research priorities?

Fred Bonte: Looking around at what had happened to the field of nuclear medicine while I had been away from it for eight years I found that one of the most exciting developments was three dimensional imaging. An old friend of mine, David Kuhl, (now at the University of Michigan) actually made the first three-dimensional images with radioisotopes and with transmitted radiation as well, for which he hasn't got nearly the credit he's deserved. The concept of imaging not only anatomy but the body's physiologic activity in three dimensions was intriguing. While I was gone, x-ray CT scanning had been invented, and clearly had contributed very significantly to the study of disease just by the ability to study anatomy in a three dimensional mode. The thought of being able to study other functions in three dimensional

and maybe even dynamic modes was very attractive. So we enlisted tomography as the modality that our new center would experiment with.

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John Kuranz, PhD

JOHN KURANZ WAS A GRAD student at the University of Chicago when the U.S. entered World War II. The Army drafted him for a top secret project that would culminate in the control of nuclear energy–and the first atomic bomb. Deeply impressed with the potential of the new energy source, especially in medicine and biology, at the age of 25 he founded Nuclear Chicago Corporation in 1946, one of the first manufacturers of nuclear instruments and radiochemicals. He went on to earn a doctoral degree in physics from the University of Southern California in 1957, chaired the Atomic Energy Commission's Committee on Isotope Development from 1962 to 1968, and led the nuclear chemical division of Amersham Corporation from 1968 to 1972. Dr. Kuranz is now chairman of the board of Amersham's Medi-Physics, Inc., and a senior advisor of Siemens Gammasonics.

Newsline: Do you recall what sort of expectations you had at the outset of the emerging atomic era?

John Kuranz: Right away some of us physicists working on the Manhattan Project realized that even if the weapon didn't work, we knew we could do some really marvelous things in medicine and biology. Therapy with iodine gained the most attention at first. As a physicist though, diagnosis based on radiotracers excited me most since it would require the development of new instruments. By the early '50s it was clear that diagnostics would be very important.

At Nuclear Chicago, we operated on the premise that whatever needed to be monitored metabolically, you could hardly improve on the nuclear tracer method for sensitivity. That's been true until very recently. Nuclear medicine was right on the leading edge of using this new technology.

Newsline: Do recent advances in non-nuclear diagnostic imaging modalities threaten to supersede nuclear imaging?

John Kuranz: In structural imaging, magnetic resonance already outperforms nuclear imaging. But in studying function, one still can't beat nuclear medicine. MR may match nuclear medicine eventually, I think, but new scientific efforts in nuclear medicine are moving forward. Nuclear medicine is already moving in the direction of therapy.

Newsline: Why is therapy only now emerging as a significant part of the industry?

John Kuranz: Ways of directing radioisotopes with great specificity are just now reaching the application stage. Monoclonal antibodies are stirring a lot of interest. Several bone-seeking agents are nearly ready for marketing as well, after years of basic research and clinical trials. Because the therapy agents can be directed with precise specificity, and because they emit local energy and can be monitored, these new products come close to being ideal as a treatment method.

Newsline: Compared to other challenges in this industry, how important is isotope supply?

John Kuranz: Without isotopes, how can you have nuclear medicine? Nuclear medicine today relies on too many of the same old radiopharmaceuticals. Not enough is being done to develop new isotopes for new uses. I would like to see the U.S. again be the unchallenged leader in research applications of nuclear medicine. We aren't any longer. There is so much potential going unexploited in the U.S.

Newsline: North America depends entirely on Canada's Nordion International for molybdenum-99. Do you consider a domestic supplier important for the U.S.?

John Kuranz: In terms of global dependability for nuclear medicine, we need more sources. Our current supply is adequate in quality and quantity, but depending on one source is not comfortable if that source should be forced to shut-down for some reason.

Newsline: What chances do you give the Energy Department effort to produce molybdenum at Los Alamos National Laboratory in New Mexico?

John Kuranz: I don't think the DOE effort is likely to succeed at all in the short term. Amersham and other major vendors are working on securing alternate suppliers.

Newsline: What did you learn, travelling in Russia earlier this year,

about their isotope-production infrastructure?

John Kuranz: They understand advanced technology, are dedicated people, and they are very competent technically. But the Russians are very naive in business and have no way to bring products to the market, although I think they are learning fast. We're trying to tap their nuclear and chemical expertise for developing biomedical applications. Russian technology could go elsewhere, and not into health care, if you know what I mean, exacerbating the problems of nuclear weapons proliferation. One aim of Amersham is to arrange cooperative relationships with scientific centers in Eastern Europe, primarily in Russia.

Newsline: Amersham was perhaps the first Western companies to strike a business deal for scientists and facilities at Chelyabinsk, a once secret weapons laboratory of the former Soviet Union. Will Chelyabinsk be used to make isotopes for nuclear medicine?

John Kuranz: I visited the facility and the Russians have at least four high flux reactors of the type at Chelyabinsk that are rather ideal for producing isotopes. Much of the world's supply of carbon-14 and tritium for the life sciences comes from Chelyabinsk.

Newsline: What about stable isotopes, such as the strontium-88 needed to make strontium-89 radiopharmaceuticals for treating bone metastases?

John Kuranz: The raw materials for any major radiopharmaceutical are an issue for concern, just as with moly-99. We currently have a significant stockpile of strontium-88, and in the foreseeable future, there will be no problem, but we want to prevent the situation like the moly one, so we are looking into a series of options, DOE facilities, possibly Russia, or other international facilities, or even some technology driven sources not currently available.

Newsline: What has it been like to see the nuclear medicine industry evolve to where it is now?

John Kuranz: One really can't deny that nuclear medicine has been a giant benefit for humanity. For me, playing just a small part in that has been a tremendous uplifting experience. ■

Arthur M. Weis

FOR ENGINEERS SUCH AS Arthur M. Weis, the promise of nuclear energy was limitless following the second World War. The coming atomic age meant thousand-megawatt nuclear reactors powering not only homes and cities but desalination plants that would turn earth's deserts into vast farmlands. Mr. Weis joined the nuclear business 45 years ago as an aerospace engineer assigned to nuclear aircraft propulsion. Later work included development of nuclear batteries of the type used to generate electricity aboard deep space probes, for which he holds a patent. For almost 30 years now, his firm Capintec, Inc., has been making radiation dose calibrators and other instruments for nuclear medicine.

Newsline: How did you manage to jump from aerospace to nuclear medicine?

Arthur Weis: In the early 1960s I had gone off on my own to found Capintec, originally as a consulting firm primarily to countries interested in developing nuclear energy–when you were an American nuclear engineer in those days, people recognized that you had state-of-the-art knowledge of all things nuclear. Around '65 we were on the lookout for all kinds of applications for nuclear instruments and materials and some of us took an interest in the emerging medical uses of radioactivity. Our job was to choose promising technologies, help develop them, and get companies like Nuclear Chicago and Picker to take on manufacture and marketing. We just delved deeper and deeper into nuclear medicine. A dose calibrator became our major entree into the field and everything else fell by the wayside. There was no strategic plan or anything like that. I would never have thought 30 years ago that nuclear medicine would become a daily diagnostic procedure in every hospital.

Newsline: Did you ever produce medical imaging devices?

Arthur Weis: The spark chamber, conceived by a French Physicist in the CEA [Commissarit a l'Energie Atomique], which lost out to the Anger camera as the instrument of choice. Capintec introduced it in the 60s, and its still a great idea, but it never took off. Radioactivity would ionize the gas sealed within the spark chamber, which would trigger an avalanche that would create a discrete image. No crystals, no PM [photomultiplier] tubes–much simpler and inexpensive–a great idea.

Newsline: What trends in instrumentation do you foresee?

Arthur Weis: The future of nuclear medicine obviously is dependent on the development of new radiopharmaceuticals, but you can't compete with static imaging modalities like CT and MRI. You've got to be able to do things that they can't and do them very cost effectively. That means reliance not so much on pretty pictures but useful information. I support Henry Wagner's views that simple, affordable probes yielding important information about the processes of kidney function, say, in an organ transplant, or brain receptors in a patient in rehab for drug addiction, will play an important role in the increased utilization of nuclear medicine procedures.

Capintec has a number of probe type systems that clinicians are experimenting with. If one works out, we'll manufacture it.

Newsline: In a world where the word "nuclear" looms so fearfully in many people's minds, do non-nuclear imaging modalities have an unfair advantage?

Arthur Weis: When CT came along, everyone said nuclear medicine is done because no one is going to want to use radioactivity in medicine. The same was said when MRI came along but nuclear medicine is still going strong. The use of radioactivity in medicine will outlive me and you because there are no serious challenges to the use of these procedures.

The future of nuclear medicine procedures is so bright, in fact, that we have to face up to the challenge of other specialties trying to seize control of nuclear medicine studies. Orthopedists want strontium-89 and the other radiopharmaceuticals for palliation of pain from bone metastases. In nuclear cardiology, the major procurers of new equipment are not the nuclear medicine physicians, they are the cardiologists. Oncologists are saying that radioimmunotherapy is a form of chemotherapy best performed by them. Some people don't want to talk about this but you have to face up to it before you can resolve it.

Newsline: How important are the isotope supply difficulties of the U.S.?

Arthur Weis: If an isotope weren't available from Canada or in the U.S., I'm sure it could be obtained from Russia or China or somewhere else.

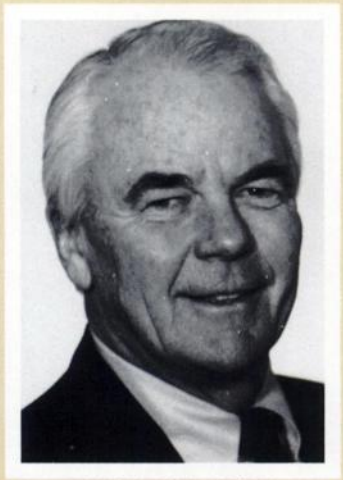
I just came back from China, where I met with people from the China Institute of Atomic Energy radioisotope department. I got the distinct impression that they were looking for ways to export their materials. By the way, they have developed their own supply of MIBI.

I do think, however, it's in our national interest to have a domestic source of these basic, important materials. If we as a country can spend $8 billion on the Superconducting Super Collider, why can't we spend the relatively small sum it would take not only to develop new types of radionuclides but also to supply isotopes for clinical nuclear medicine? Which is more important to the U.S.A.? To mankind?

Years ago, when I was working with the Atomic Energy Commission's division of isotope development, under Paul Aebersold and then with Ernie Tremmel, one would have never even thought that we would become dependent upon foreign suppliers, including Canada, for the most important basic isotopes such as molybdenum-99. Unfortunately, the Department of Energy has stumbled in trying to reverse this situation, probably because the department ranks isotope supply lower in priority than, say, the human genome project.

Newsline: Do you expect government plans for health care to hurt high-tech specialties like nuclear medicine?

Arthur Weis: I believe that there is a great future for nuclear medicine because it continues to be a very cost-effective way of getting information about metabolic processes. I think CT is going to have a tough time. Cardiac catheterization is going to have a tough time. But I'm very bullish on nuclear medicine. I've always been mystified at how the radiologists could have so successfully promoted the MRI and CT concepts in this country at the expense of nuclear medicine. You get much more for the money out of the nuclear medicine modality than you get out of either MRI or CT. ■



Wil B. Nelp, MD

BEFORE HE BEGAN TRAINING in 1960 in nuclear medicine at the Johns Hopkins Hospital in Baltimore, Wil B. Nelp, MD, had the chance to attend that year's Annual Meeting of The Society of Nuclear Medicine. "The people at Hopkins told me I could go to the meeting as long as I promised to attend every session, take good notes, and report back on everything that happened," Dr. Nelp recalls. The young internist, goaded by his friend Henry Wagner, Jr., MD, saw exciting opportunities. "I didn't have an expansive view of what was ahead, but I thought it played to my strengths," Dr. Nelp says. A prolific researcher whose career spans three decades,

Dr. Nelp has since 1962 headed the division of nuclear medicine at the University of Washington School of Medicine. There he has forged one of the preeminent nuclear medicine training programs in the world.

Newsline: Obviously hundreds of new radiopharmaceuticals have been developed in the past 30 years, but has the process evolved much since 1960?

Wil Nelp: In the 1960s, radiopharmaceutical development often consisted of sitting down with a chart of radionuclides, checking to see which ones were available and then trying to figure out what you might try to do with them. If something looked promising, you'd try it. Today radioparmaceutical chemistry has advanced to the point where one can start with a tracer in mind that could go to a specific organ or delineate a specific function and then design that radiopharmaceutical.

Newsline: You were one of a handful of investigators who pioneered in vivo activation analysis—how did that come about?

Wil Nelp: In vivo activation analysis, one of the things I'm proud of, was unique to my laboratory and to one other group at Brookhaven National Laboratory. We were interested in measuring bone mass in people with osteoporosis and we developed a system in which we could actually spray a person with neutrons that would make some of their bone calcium become radioactive. With a whole-body counter we could measure the amount of radiocalcium, which is directly proportional to the total amount of calcium in the person's body. With this technique we could measure the grams of calcium within 3% and test experimental drugs intended to inhibit loss of calcium from the body.

The program evolved into an osteoporosis research center within the division of nuclear medicine, although we've just recently stopped doing in vivo neutron activation in favor of dual photon absorptiometry. Regional calcium measurements are pretty representative of the whole skeleton.

Newsline: More recently, you've made important advances in treatment of cancer with radiolabeled antibodies.

Wil Nelp: We have a major team effort with oncology, nuclear medicine, and immunology looking at several long-term treatment protocols for adult leukemia and lymphoma using high-doses of radiolabeled antibodies. Conventional therapy for this group of diseases has about a 50% failure rate. From a group of people with lymphomas that did not respond to the conventional treatments, we've treated 20 patients so far with escalating doses. The doses are large enough that the bone marrow is completely obliterated so you have to harvest bone marrow before treatment and then give it back to the patient shortly after treatment. Of these 20, 17 have gone into complete remission, and 9 are still in remission as long as five years. One reason the work looks so good is that lymphomas are extremely sensitive to radiation.

We've spent a tremendous amount of effort at the basic science level, asking questions such as how much radiation can you give without destroying normal tissues other than bone marrow. We've administered the highest doses of radiolabeled antibodies of any laboratory in the world, up to 800 mCi.

Newsline: What trends do you envision in radioimmunotherapy?

Wil Nelp: I think the antibody concept is going to blossom, but I think we'll completely replace murine antibodies. We're going to have genetically or chemically engineered antibodies and customized peptides. The first diagnostic antibody recently approved by the FDA is going to look fairly old fashioned in ten years.

Newsline: Why do you think nuclear medicine investigators have so such strong interest in treating cancer?

Wil Nelp: Medical oncologists have been doing much the same thing for many years, i.e., administering fairly non-specific chemotherapeutic agents. Radiolabeled antibodies for therapy present a lot of opportunity, and there's a lot of interesting work to do. We're a long way from successfully treating other solid tumors with antibodies, so it remains a challenging area.

Newsline: With the advances being made in radiopharmaceutical therapy, do you think diagnosis will recede in importance in nuclear medicine?

Wil Nelp: Not anytime soon. Remember, there has not been a therapeutic isotope licensed in 30 years. Maybe one therapeutic isotope for the treatment of bone pain from cancer metastases will be approved soon, but that's all that's on the near horizon. The challenges to clinically perfecting these agents are still sitting there squarely facing us. The antibody and labeled bone-seekers have put emphasis back on therapy, but do not expect nuclear medicine world to turn into a therapeutic discipline.

Newsline: Does the new President's emphasis on health care reform present opportunities for nuclear medicine?

Wil Nelp: I think there will be opportunities for nuclear medicine in terms of cost savings. For example, a recent article in JNM compared the value of MRI versus a nuclear medicine procedure for a specific diagnosis and found the two to be equivalent, but MRI is three times more expensive. Thus, by selecting the least expensive exam, there would be cost savings. But I'm not sure that such rational analyses are the way that political decisions about health care reform are going to be made.

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Bonte Interview
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Newsline: And you have taken a keen interest in using tomography to diagnose Alzheimer's disease.

Fred Bonte: That's right, I'm principally interested at the moment in the differential diagnoses of dementias in cooperation with our Alzheimer's disease research center. I realize the fearsome problem that the dementias are going to represent medically. As the population ages, the dementias are going to come into focus as one of the principal health threats in the country. Alzheimer's, like AIDS, has no cure. The patient becomes progressively demented, and when the family won't be able to take care of him anymore, he may have to live in a semi-vegetative state in a nursing home for years and years under very expensive circumstances. Any contribution that can be made to the management of this group of diseases must be made.

Newsline: How far has your work progressed?

Fred Bonte: We've now used SPECT brain blood flow imaging prospectively, that is, we've imaged the patient as he or she is admitted to the Alzheimer's center and we make a blind diagnosis. At the same time the clinical psychologist, psychiatrist, and neurologist are making a clinical diagnosis. We've studied well over 300 patients now, and some of them are beginning to come to autopsy.

Newsline: With no cure, how useful is such a diagnosis?

Fred Bonte: Out in the community, SPECT is helping the referring physician by first sorting out the patients with Alzheimer's. And now some palliative treatments are coming out, a drug called Tacrine for example, that may help ameliorate symptoms temporarily.

But there is a large catalog of other diseases that produce dementia, some of which are treatable, and a few that are curable such as the dementia caused by vitamin deficiency. If you can find the origin of the emboli that cause multiple infarct dementia–sometimes it's a defective heart valve, for example–and correct it, then the shower of emboli will stop and the disease won't progress. Neural syphilis is making a big comeback after 25 years, this time in immune compromised patients. With treatment, you can stop the process and some people behave as if you can even reverse it. So its important to sort out the various dementias.

Needless to say, if there are any treatments developed that are capable of reversing any of the changes wrought by Alzheimer's disease or other dementias, then you ought to be able to detect such reversals with serial brain blood flow studies.

Newsline: What other directions in nuclear medicine do you expect to become important?

Fred Bonte: I've gotten involved with our radiologists in what you might call interventional neuroradiology. We have a couple of gifted people who can put a catheter into anything, and once they've got it there they can introduce things to block vessels into tumors, to fill up aneurysms with substances that will clot the vessel shut and relieve dynamic flow problems that deprive otherwise normal brain of its blood supply. An easy way to predict what the circulatory pattern is going to be if you sacrifice a vessel is to run a balloon catheter to the spot where you want to obstruct the system and expand the balloon. At that point we inject a tracer, usually HMPAO, and when the radiologist is finished, the tracer remains in its original distribution for a few hours representing what blood flow would be if the vessel were sacrificed. This is going to be a growing area of brain blood flow SPECT, its contribution to interventional neuroradiology.

"I realize the fearsome problem that the dementias are going to represent. As the population ages, the dementias are going to come into focus as one of the principal health threats in the country."

Newsline: Some people have warned that the specialty is in danger of fragmenting out of existence. Do turf battles between nuclear medicine and other specialties disturb you?

Fred Bonte: People have pronounced nuclear medicine dead on several occasions since I got into it in 1946, only to see it make some giant step forward with the development of new modalities, new concepts, new ways of looking at things and making contributions to medical care. It's still around and still very healthy, and still making very highly significant medical contributions, so I see it having a pretty good future. At my age, I can't afford to get out of it anyway [laughs]. You get a lot more done if you work with other specialties in a cooperative effort. The Alzheimer's research center here is made up of people form about seven different disciplines. The sort of informal group that is doing these interventional studies is made up of people from neurology, surgery, radiology, and nuclear medicine. Ultimately we'll have pathologists involved too. ■

Nelp Interview
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Newsline: Of the many challenges the field faces, which do you find most urgent?

Wil Nelp: One of the major challenges is to keep the focus on good academic training programs. Of everything I've been involved with in this field, I'm probably the proudest of the residency training program we have developed here at the University of Washington. We've had a very successful academic training program–but it requires continued evaluation, modification and, of course, effort. ■

Michael J. Welch, PhD

FEW, IF ANY, RADIOCHEMISTS had staked a career on nuclear medicine when in 1966 Michael J. Welch, PhD accepted an assistant professorship in radiation chemistry at Washington University's Mallinckrodt Institute of Radiology in St. Louis. The field had yet to give chemists cause for excitement and peers tried to warn Dr. Welch that he was making a mistake, but he believed opportunities in nuclear medicine would expand rapidly. "My expectations have come through beyond my wildest dreams," the professor of radiology and director of the division of radiation sciences at the Mallinckrodt Institute says today. Among other firsts, Dr. Welch helped pioneer ways to link extremely energetic, short-lived radionuclides to biomolecules now routinely used in positron-emission tomography.

Newsline: The whole approach to radiopharmaceutical research must have changed drastically over the last 30 years.

Michael Welch When I joined the field, radiopharmaceuticals were developed by what you might call the shake-and-bake approach–compounds were labeled and then injected into animals to see where they went. With the current generation of radiopharmaceuticals, a lot of thought and logic goes into the chemical design from the outset. It is fast becoming a completely rational process directed at a known result. The science is two orders of magnitude more sophisticated.

On the other hand, 20 years ago you could develop a new compound with a radiochemist in a lab more or less by yourself. To make a contribution in 1993, you really need a team of specialized people. If you're working with positrons, you need sophisticated organic chemists. With indium compounds, you need inorganic chemists who know how metals bind to molecules, and so on.

Newsline: What is a good example of the new rationally designed drugs?

Michael Welch: There are all sorts of peptides with which one can map body processes, tumor growth for example. These tracers allow planning of what sort of therapy you can expect to succeed. A lot of these compounds are only just beginning to be developed.

One of the most exciting developments in the last couple of years is the indium-labeled octreotide (Octreoscan, Mallinckrodt Medical, Inc.) developed by a group of investigators in Rotterdam. It's undergoing review by the Food and Drug Administration. They started with the somatostatin peptide, made a non-metabolisable analog, knew where you could put large groups such as DTPA, and went from there.

A similar effort is the estrogen work that we're doing. The least invasive way to treat breast cancer is with anti-estrogen therapy. You can use a positron-labeled estrogen, which we developed with J. A. Katzenellenbogen of the University of Illinois, to predict the success of such therapy. Again, from sophisticated chemistry studies, one knows where on the molecule you can put bulky groups and this has now been done to produce technetium-99m labeled steroids.

Labeled androgens could be similarly used in people with prostate cancer, labeled progesterone for breast cancer, and other hormones which you can use to predict what sort of treatment is likely to succeed. Then you can use the labeled compounds to monitor the effects of the therapy.

Newsline: Will this type of work become a prominent part of nuclear medicine?

Michael Welch: Nuclear medicine is going to play a major role in the next 20 years in oncology. Before long we'll be using oligonucleotides, anti-sense agents–all these colorful terms used by molecular biologists refer to molecules that can be utilized to make radiopharmaceuticals. The applications for such compounds are likely to be largely in oncology, looking for problems with genetic expression. It may seem a bit far-fetched, but if you went back 20 years and said you could map dopamine receptors and estrogen receptors using nuclear medicine, people would have considered that far-fetched.

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Welch Interview
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Newsline: With the growing emphasis on cost-containment and proving the effectiveness of medical procedures, how do you expect nuclear medicine will fare?

Michael Welch: I think the prospects are good. I think nuclear medicine approaches can play a major role in cost containment and in improving the quality of life of cancer patients in particular.

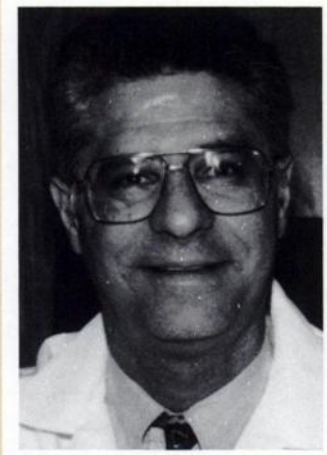
Newsline: What about modalities like PET, which on the surface at least seem prohibitively expensive?

Michael Welch: I'm not certain that PET is going to fare very well in many of the applications currently being touted. Some indications will be important right away, showing surgeons what they should do for epileptic surgery, directing approaches to treating heart disease. Most other applications, including oncological tests, have to mature another five or ten years.

People are trying to make PET less expensive. I have a collaboration with a company in Boston (Science Research Laboratories, Inc.) that's trying to manufacture a low cost accelerator. To me its obvious you can make the isotope production end less expensive. Some companies have already been able to make less expensive PET cameras. I'm not sure that scaling up a triple-headed SPECT camera with special heavy collimators for positrons will wind up more affordable than scaled down PET cameras.

Newsline: You seem quite optimistic about opportunities for investigators in the field.

Michael Welch: Looking at the potential of rationally designed radiolabeled peptides, receptor ligands, and now oligonucleotides, how can you be anything but optimistic? ■



Barry A. Siegel, MD

BY BLIND LUCK, HE SAYS, Barry A. Siegel stumbled into an elective in nuclear medicine during his sophomore year in medical school. His first choice was the cardiac radiology elective, but others had beaten him to it, so he signed up to work for E. James Potchen, MD, the new director of nuclear medicine at Washington University in St. Louis. The day after completing his residency at the university's Mallinckrodt Institute of Radiology in 1973, Dr. Siegel succeeded Dr. Potchen as director of the division of nuclear medicine, a post he has held ever since. In Dr. Siegel's active research career he has authored or co-authored nearly 200 scientific articles, reviews, and books. He has been an advisor to the U.S. Food & Drug Administration for over 20 years and has chaired the Advisory Committee on Medical Uses of Isotopes of the U.S. Nuclear Regulatory Commission since 1990.

Newsline: Do you remember your first nuclear medicine experiment under Dr. Potchen?

Barry Siegel Jim Potchen set me up doing an experiment on pancreatic scanning, trying to increase the uptake of selenomethionine. We fed rats raw soybeans, which contain a trypsin inhibitor that interferes with the digestion of protein. After a couple of weeks sure enough the uptake of the tracer increased. It certainly wasn't a very practical technique, but it got me really turned on to the idea of using the tracer method to measure human physiology.

Newsline: What was it like working at the Armed Forces Radiobiology Research Institute in Bethesda, Maryland, during your two years with the Air Force after medical school?

Barry Siegel AFRRI is an arm of the Defense Nuclear Agency–the primary goal of DNA was to learn about the effects of nuclear weapons on living cells and animals. What they did for many years was study weapons effects using fast neutrons and thermal neutrons, high doses and low doses to learn more about the things we were afraid of during the 1950s, you know, 'duck and cover'. By the 1970s those experiments had become passe and AFRRI expanded its facilities to examine other types of trauma with military relevance. Along with that they established a nuclear medicine laboratory equipped with a couple of gamma cameras, hired a radiopharmacist and technologists experienced in working with animals.

During the time I owed the Air Force I filled in the slot that opened for a nuclear medicine physician. My job description for two years was 'do research'. I was almost unconstrained in what I could do–as long as I showed some relevance to the Department of Defense mission. I did some research that I'm proud of, investigating the effect of uptake of bone-seeking radioactive tracers on bone blood flow.

Newsline: What have been the most profound changes in the way nuclear medicine is practiced since you began?

Barry Siegel: The biggest change has been the rate of change. The most amazing thing about nuclear medicine is that in any given five year period, what you do for a living is completely different from what you did in the previous five years. I was at one time incredibly adept at reading conventional brain scans, but now I haven't even looked at one for years.

As new technology has come along, things that we counted on as our bread and butter have entirely disappeared and we have had to learn new things. Jim Potchen used to joke that the reason nuclear medicine continued to advance is that we can figure out new tests faster than clinicians can prove they're not useful. As other imaging techniques become more powerful, we're going to have a harder and harder time documenting that what we do can make a difference.

Newsline: You've been advising the FDA ever since the agency began regulating radiopharmaceuticals in 1972. Has the agency evolved much in this time?

Barry Siegel: In 1972, when the FDA was about to take over responsibility for a large number of drugs from the Atomic Energy Commission, manufacturers just had to prove that they were able to get an image of the target organ. If the agent was supposed to be a diagnostic radiopharmaceutical for pancreas scanning and if it made a picture of the pancreas, then it was effective. That's a very low form of efficacy by today's standards. The FDA has become much more rigorous in establishing the safety and efficacy of new radioactive drugs. Now a manufacturer has to show that its product provides reasonably accurate diagnostic information. The next stage, although we haven't quite gotten to this yet, will be having to prove that the drug actually influences patient outcome.

Newsline: Why do you expect that?

Barry Siegel: Much of what we do, we do without knowing if it makes a little bit or a lot of difference. The imaging specialties, I don't think they are adept at knowing how to prove that techniques have a positive impact on the care and improvement of a patient's condition.

It's a lot easier to do this type of analysis with therapy, I mean, how can you really assess the impact of what happens if you do or don't do a diagnostic test?

Newsline: Some investigators have expressed a yearning for the FDA to approve radiodiagnostics on the basis of whether they provide physiological information and let the physicians decide if it's useful in diagnosis.

Barry Siegel: People think it would make their life easier, but it runs counter to the grain of current medical thinking. The assumption is that the market place will be efficient in directing the use of diagnostic tests. Now in my heart of hearts I would like to believe that the market is reasonably efficient, but most of the evidence doesn't support me.

Diagnostic tests are often done just out of habit, or for defensive reasons, or even because they've become little gold mines for a clinician. Specific indications for radiopharmaceuticals are a little more linked to the outcomes concept. Although I like the concept of general indications, I think it's unlikely to happen.

Newsline: Do you see much promise in labeled antibody diagnosis and therapy?

Barry Siegel: I'm interested in evaluating approaches to tumor staging with PET and comparisons of FDG-PET with monoclonal antibodies.

Whether monoclonal antibodies will ever come into widespread use remains to be seen. I'm very interested by recent developments in several small peptides as biologically specific markers that bind to specific receptors and that clear from the circulation rapidly, unlike antibodies. Octreotide is an example, which I hope the FDA approves soon. It's an amazingly simple, straightforward compound that goes after a large number of tumors.

The presence or absence of the type of receptors that it binds to tells you important information about how to treat the tumor. This type of strategy is going to yield fruit for nuclear medicine.

Newsline: So you see some fundamental changes ahead for nuclear medicine.

Barry Siegel: We're already getting knocked out of the box by other anatomical-type studies, and when somebody gets around to building a reasonable, fast, whole-body MRI machine, the mainstay of nuclear medicine, namely the bone scan, could be out the window.

Recently I've been reading articles suggesting that we've probably come about as far as we can with radiation and chemotherapy. The next step will be biological agents that modulate the behavior and growth of a tumor rather than just trying to kill it.

Nuclear medicine will be able to do things along these lines, assuming we can afford it. If we as a country decide that 14% of GNP is too much I don't think we will be able to afford some of these new tools.

Newsline: Looking back, are you satisfied with the specialty that you, as you said, "stumbled" into?

Barry Siegel: I'm probably proudest of the 80-some residents I've trained over the years who've gone on to be capable clinicians. I didn't envision getting so involved in the affairs of government, but I've even enjoyed that. I love my career–I work too hard, but I'm having a great time and I plan to keep on doing it for a long time. ■