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UNIVERSITY OF MICHIGAN
DEPARTMENT OF RADIOLOGY

NEWS AND NOTES

ISSUE 6 FALL 2013

CELEBRATING 100 YEARS OF RADIOLOGY AT U-M

A Distinguished Past & A Pioneering Future

Looking Back

Academic radiology got its start at U-M in 1913 when Dr. James Van Zwaluwenburg became the first professor of roentgenology in the nation. Shortly thereafter, he became chairman of the first university department dedicated to this nascent medical specialty.

Perhaps unsurprisingly at a university so drawn to innovation, the use of X-rays had actually begun several years earlier, just months after Wilhelm Röentgen announced his discovery. In April 1896, Henry Carhart, a professor of physics, and William Herdman, a professor of electrotherapeutics, used the technology to image a bullet in a patient's foot. However, until 1913, X-ray imaging was offered merely as a service with no formal instruction.

All that changed with Van Zwaluwenburg's appointment, and U-M swiftly embraced the clinical, educational, and research aspects of this promising diagnostic field. The Department of Radiology has had seven chairs in the last 100 years, all of whom guided the department in developing its infrastructure, exploiting the field's emerging modalities, melding its diagnostic and therapeutic capabilities, and training its future leaders. A history of each chair's tenure is available here.

Since that time the department has achieved world-class status and has made significant contributions to the field (see p. 4).

Under the stewardship of the current chair, N. Reed Dunnick, MD, the department logged another important "first" – becoming first in NIH funding in 2003. In the top five every year since, the department features a deep and diverse research portfolio that is driving the field on a variety of fronts.

Looking Forward

A technology-based field like radiology is thrust almost continuously into new planes of discovery with the advent of each new modality. However, as Dunnick explains, during his

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LETTER FROM THE CHAIR

Dear Michigan Radiology Alumni, Friends, and Family:

We have just completed another outstanding academic year. All senior residents passed their oral board exams with flying colors and 28 fellows completed their training at the end of June. On a national scale, although ACGME approval is still needed, the American Board of Medical Specialties (ABMS) approved a new primary residency in Interventional Radiology. The fellowship in Interventional Radiology will be phased out over the next several years. Our new Director of the Division of Interventional Radiology, Wael Saad, MD, has been one of the leading proponents for this new program. Mike DiPietro, Kate Klein and Leslie Quint are doing an outstanding job with medical student education and Kate has taken the lead in reinvigorating our radiology interest group among the medical students.

In November, we installed a new intraoperative magnetic resonance scanner in one of the operating rooms of the new Mott Pediatric and Von Voigtlander Women's Hospital. We are using it for both pediatric and adult patients for intracranial neurosurgical procedures, and our volume of cases has already exceeded our expectations. This is a major advance in the care of these patients as it allows surgeons to review the results of their work prior to closing the operative field.

High-Intensity Focused Ultrasound (HIFU) is a new technique that allows us to locally heat and destroy tumors. This minimally invasive therapy has been used elsewhere to reduce the size of uterine fibroids but has many other potential applications in the prostate gland, liver and kidney. When we upgraded our 3T MR scanners at University Hospital, we added the capacity to perform these HIFU procedures. We are doing initial work on phantoms, but hope to be applying this to patients by the end of this summer. Peter Liu has taken the lead on this project and is assisted by Tom Chenevert and Dariya Malyarenko in MR, Brian Fowlkes and Oliver Kripfgans in ultrasound, and Jonathan Rubin and Elaine Caoili for clinical applications.

Our research programs remain strong and we were once again ranked 4th in the nation for NIH funding among university radiology departments. The North Campus Research Complex (NCRC) continues to add new investigators every month. Many of these will need sophisticated imaging and we are planning our research imaging core now. Brian Fowlkes, in his role as Associate Vice President for Research in Health Sciences, is leading this effort. When fully outfitted, we expect to have a full range of imaging modalities including magnetic resonance, computed tomography (CT), ultrasound, radiography and nuclear medicine.

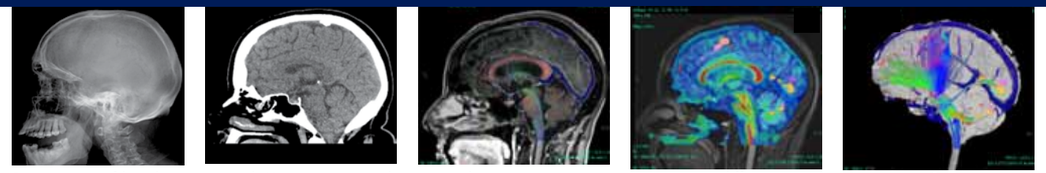
As our Medical Center continues to grow, we are adding new outpatient facilities to make it more convenient for our patients and to avoid further congestion in the hospital complex "on the hill." By July 2014, we expect to open a new facility in Northville, Michigan which will have primary care and specialty clinics, and our imaging core will include magnetic resonance, ultrasound and radiography.

I hope to see all of you at our reunion October 3-5, 2013, as we inaugurate the William H. Beierwaltes Memorial Lecture, celebrate our first 100 years of radiology at the University of Michigan and beat Minnesota in the Homecoming football game.

GO BLUE!!!

Regards,

M. Reed Dunnick, MD



Progression of head imaging with X-rays, computed tomography, magnetic resonance imaging, diffusion tensor imaging, perfusion imaging, functional MRI and 3D model showing fMRI and tractography. Photo courtesy of Gaurang Shah, MD.

Continued from page 1

tenure the field has been transformed by an advance perhaps as revolutionary as Röentgen's discovery itself: molecular imaging.

"Medical imaging has been depicting gross anatomy for years," says Dunnick, "and we do that very nicely. But what's likely to shape the future is our ability to interrogate at the cellular level. We can use nuclear medicine, of course, but also MRI and optical imaging, to see what is happening inside the cell."

This ability to image the molecular pathways involved in cellular function has profound implications for pharmaceutical development and the early detection and treatment of disease.

"A good example," says Dunnick, "is assessing the effectiveness of chemotherapy. Traditionally we'd begin a patient on chemo, then three months later, take an X-ray or computed tomography (CT) scan. But a tumor might have to double in diameter before we'd know the therapy wasn't working. By then it has increased eight times in volume, and the patient may not be recoverable. Whereas if we can use molecular imaging to see how cells are handling the chemotherapeutic agent, we can predict how it's going to work within weeks and switch the patient to something else if needed."

Researchers across the department are leading such efforts. Among them are Professors Brian Ross, PhD, and Thomas Chenevert, PhD, experts in magnetic resonance imaging and spectroscopy (MRI/S). They have collaborated on research using MRI to track the diffusion of water through tumor cells as an indicator of chemotherapy response. Because cancer cells slow the diffusion of water, an increase in diffusion correlates to a positive response to therapy. Their approach has been validated by other labs and used successfully in a variety of tumor types. Their next step is a multi-center brain tumor clinical trial.

Similarly, Chief of Nuclear Medicine Kirk Frey, MD, PhD, was involved in a study designed to determine if positron emission tomography (PET) could be used to assess the effectiveness of radiation therapy for lung cancer. Because radiolabeled glucose (FDG), is taken up disproportionately by cancer cells, scans showing a decrease in FDG uptake signal a positive treatment response. A recent pilot study suggests that a scan just weeks into treatment can inform doctors whether to stay the course or change their treatment plan; larger studies are now underway.

Of course, the potential of molecular imaging goes well beyond cancer treatment. Frey and his colleague, Professor Nicolaas Bohnen, MD, PhD, are using PET to study molecular activity in the brains of patients with Alzheimer's and Parkinson's disease, respectively. Frey has used PET scans to help differentiate various types of dementia (see p. 12), an important step in both prescribing and evaluating drug regimes.

For his part, Bohnen studies the role of the neurotransmitter acetylcholine in Parkinson's disease. While most research emphasis in Parkinson's has been on the neurotransmitter dopamine and in Alzheimer's on acetylcholine, Bohnen has switched things around with intriguing results. Using U-M-developed radiopharmaceuticals, he's shown that lower levels of acetylcholine in specific brain regions negatively associate with motor control, including poor balance and slower gait speed, in Parkinson's patients. He's now working with a new PET radiotracer synthesized by U-M's cyclotron facility (see p. 10) to test a class of cholinergic drugs targeting nicotine receptors to treat mobility problems in patients with Parkinson's disease.

Another key modality in molecular imaging is optical, which is the domain of Associate Professors Gary Luker, MD, and

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Celebrating 100 Years of Radiology at U-M: Selected Milestones

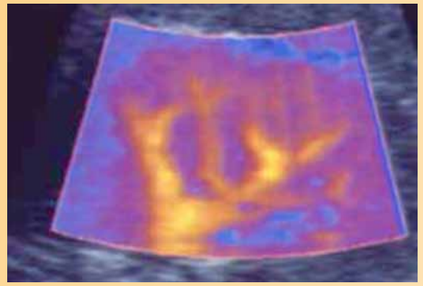
IMAGING THE ADRENALS: NP-59 & MIBG

U-M is recognized worldwide for its expertise in diagnosis and therapy for adrenal disease, and an early aspect of this was its role in developing the first adrenal imaging agents, NP-59 and MIBG. Far from a serendipitous discovery in the lab, these agents were the fruits of infrastructure built through the '50s and '60s by former Chief of Nuclear Medicine William Beierwaltes, MD (see p. 6). By leveraging resources available through the Michigan Memorial Phoenix Project, which provided the lab facilities needed to synthesize novel radiopharmaceuticals, and one of the first dedicated NIH nuclear medicine training grants, "Dr. B" was able to attract top-tier radiochemists whose interests and expertise dovetailed perfectly with those of groundbreaking U-M endocrinologists like Jerome Conn, MD.

One of these chemists was Raymond Counsell, PhD, who developed the first agent capable of imaging the adrenal cortex, ^{131}I-radiocholesterol. With the 2-D nuclear imaging technique of scintigraphy, U-M researchers were able to distinguish different forms of Cushing's and Conn's syndrome, and to differentiate benign from malignant adrenal cortical tumors. This work formed the basis for a second-generation adrenal imaging agent, NP-59, which U-M produced and distributed to medical centers throughout the U.S.

Another distinguished radiochemist was Donald Wieland, PhD, who created metaiodobenzylguanidine (MIBG), the first successful adrenal medulla imaging agent. Labeled with iodine-123 for diagnosis or iodine-131 for radiotherapy, it localized to adrenergic tumors anywhere in the body including pheochromocytomas and neuroblastomas. "One of our nuclear medicine physicians, Dr. James Sisson, put substantial effort into using this agent for therapy," says Professor Milton Gross, MD, who is chief of nuclear medicine at the VA. "He showed that we could treat pheochromocytomas with high-dose MIBG and improve the well-being of many patients. Even now, MIBG is a standard of care for neuroblastoma, a devastating pediatric tumor. It's the perfect example of transitioning an idea from the lab through clinical development to commercialization and patient care." It was also a key milestone in making nuclear medicine at U-M what Gross calls "the world-respected entity it is today."

DISCOVERING POWER DOPPLER



Power Doppler image of a kidney made on the machine Dr. Rubin first used. Image credit: Jonathan Rubin, MD, PhD.

> "My whole kidney lit up. The sensitivity had improved three-fold. I could see these small branching vessels that were completely invisible before."

Professor Jonathan Rubin, MD, PhD, has spent a good part of his career looking for what he calls Doppler ultrasound's "holy grail" – the real-time measurement of blood volume flow. Along the way, he had an insight that has put this goal tantalizingly within reach.

Rubin was an early user of 2-D color Doppler for blood-flow imaging. In its standard mode, it could estimate how fast blood was moving, but only in a single plane. What it couldn't do was measure blood volume flow or process weak signals due to "bad Doppler angles" or with a small amount of flow.

But one day Rubin realized that the "power mode" buried deep in a series of menus on one of his color Doppler scanners could be configured to solve these issues. To test it, he turned a scanner on himself. "My whole kidney lit up," he says. "The sensitivity had improved three-fold. I could see these small branching vessels that were completely invisible before."

His discovery quickly became a standard imaging technique. Rubin is now combining the two modes to crack the volume flow measurement problem. "In simplified terms," he says, "we use standard color Doppler to measure the velocities in each local area across a vessel, and we then sum each local velocity times its area to get volume flow."

Power Doppler solves the problem of what to do at a vessel's boundary, where a unit of area might have a portion inside and a portion outside the curved blood vessel. Rubin and his colleagues have developed a partial volume averaging technique that corrects for this and ensures the resulting blood flow measurements are not overstated.

"This technique will have a huge clinical impact anywhere we want to measure blood flow," he says, "from cardiac output to flow to the brain, in transplants, through the umbilical cord, and so on. The surrogate measures we are now using will soon fall by the wayside; this technique is definitely ready for prime time."

RADPEER'S™ EARLY MODEL

In 1980 as chairman of Sinai Hospital in Detroit, Professor Emeritus Philip Cascade, MD, instituted a system of peer review for evaluating missed diagnoses by department radiologists. That system formed the basis for RADPEER™, the program now used by more than 10,000 radiologists throughout the country to help fulfill recertification requirements in quality improvement from the American Board of Radiology.

Cascade's system at Sinai used a four-tier classification for missed diagnoses. Impossible and difficult cases (understandable misses), were labeled classes 1 and 2, and significant ones (those that should have been caught either most or almost all of the time) fell into classes 3 and 4. The missed diagnoses were classified using a process of blind-review consensus by department radiologists. The goal was to help radiologists learn from their mistakes and improve their diagnostic performance.

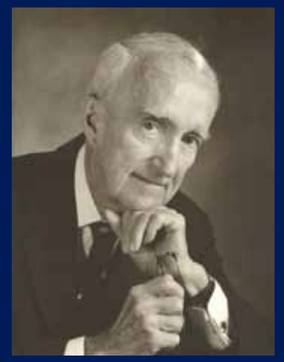
In the late '80s Cascade was appointed chair of the American College of Radiology (ACR) Committee on Quality Assurance, where he contributed the system to the ACR's new quality improvement manual. In 1991 he joined U-M as director of the Division of Chest Radiology, where he expanded and revised the system of peer review, and made it possible to compare the performance of individual radiologists. He applied the system within his division and published the results of this experience in 2001. A few years later his system became the basis for RADPEER™. "In fact," says Cascade, "our definitions of class 3 and 4 missed diagnoses are almost the same as those used in RADPEER today."

Cascade is pleased with the evolution of the system, particularly how efficiently it dovetails with routine patient care. Whenever radiologists find themselves comparing a patient's new imaging with older, previously interpreted images, they can participate in peer review by simply scoring the old interpretation and submitting the case for peer review by their radiology faculty.

Celebrating 100 Years of Radiology at U-M: Upcoming Events

Endowed Lectureship Honors Pioneering "Dr. B"

No centennial celebration would be complete without honoring U-M's first director of nuclear medicine—and a major force in the establishment of the field—William H. Beierwaltes, MD, or as he was known on campus, "Dr. B." His legacy was profound. He pioneered the use of radioiodine in thyroid disease, developed one of the first university training programs in nuclear medicine, and co-authored the first textbook on its clinical application. The training and research infrastructure he built was instrumental in developing the first radiopharmaceuticals for adrenal imaging, NP-59 and MIBG (see p. 4). His ripple effects were especially significant. "Bill was instrumental in training at least four generations of nuclear medicine physicians," says Milton Gross, MD, chief of nuclear medicine at the VA. "If you look at their pictures on the wall, you'll recognize directors of nuclear medicine at many hospitals and world-renowned researchers, scientists, and clinicians."



Dr. B. had notable success in "grantsmanship," served as president of the Society of Nuclear Medicine (SNM), and received numerous honors and awards, including the SNM's Georg Charles de Hevesy Nuclear Pioneer Award and a Scientific Achievement Award from the American Medical Association. To continue honoring his legacy, the department has instituted an endowed lectureship in his name. The inaugural lecture will be given by James H. Thrall, MD, a U-M medical school alumnus and former Division of Nuclear Medicine faculty member who worked with Dr. B. Thrall is the chairman emeritus of the Massachusetts General Hospital Department of Radiology and the Distinguished Taveras Professor of Radiology at Harvard Medical School.

100 M RADIOLOGY

WEEKEND'S EVENTS

THURSDAY, OCTOBER 3

6:30 - 9:00 pm
Welcome Reception/Strolling Dinner
Jack Roth Stadium Club: Michigan Stadium

FRIDAY, OCTOBER 4

8:00 am
CME Presentations
A. Alfred Taubman Biomedical Sciences Research Building

11:15 am
Beierwaltes Lecture

1:30 pm
C. S. Mott Children's Hospital Tour
Or
University of Michigan Museum of Art Tour

6:00 pm
Centennial Celebration
Gala Dinner: North Campus Research Complex

SATURDAY, OCTOBER 5

12:30 - 3:30 pm
Tailgate: North End Zone

3:30 pm
Michigan vs. Minnesota
Football Game

Please contact Ann Kay at annvkay@umich.edu with questions about the centennial event.

For more information, visit: radiology100.umich.edu

Share a memory

See attendees

Explore photo gallery

. . . and much more!!!

CLICK TO

REGISTER

Registration deadline is September 1st.

Your chance to take the field!

Join us at the welcome reception where you can tour the locker room and walk on the field - a once in a lifetime opportunity!!

Celebrating 100 Years of Radiology at U-M: A Timeline

A century of diagnosis, discovery, and direction

1913
- Department established under Van Zwaluwenburg

1930
- 1st Roentgenology Department in a US medical school
- Neutron therapy for cancer treatment

1940
- 1st chest x-ray surveying program in US

1950
- Michigan Memorial-Phoenix Project, producing therapeutic radioactive isotopes*

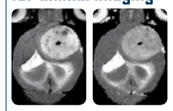
- Angiographic unit developed
- Ann Arbor VA opens

1965
- 1st fluoroscopic image intensifiers with TV monitors; allows dose reduction
- One of the 1st clinical nuclear medicine training programs in US
- C.S. Mott Children's Hospital opened

1975
- Basic Science Division created
- SPECT device "Humongotron"
- Divisions created
- NCI BCRP

1985
- Radiation Oncoloogy established as separate department
- 2 Tesla MRI/S lab for animal imaging

1995
- 7 Tesla MRI/S lab for animal imaging



- 1st power Doppler sonography

- 1st medical acoustic droplet vaporization
- Divisions by organ system rather than modality

2000
- Nuclear Medicine joins Radiology
- 1st histotripsy technology
- 1st ultrasound elasticity imaging for estimating age of thrombus
- 1st combined tomo/ultrasound
- MedSport Clinic opens

2005
- Emergency Radiology created
- Top 5 ranking in NIH funding (through today)

2010
- Cardiovascular Center opens

- Radiology Livonia Clinic opens
- 1st intraoperative MRI opens in Mott Hospital

2013

	faculty	residents	fellows
1913	1		
1930		12	
1940			
1950			
1965			
1975		39	35
1985			4
1995		65	
2000		37	17
2005			
2010			
2013		161	

- $10,000 for equipment to open dept in new hospital

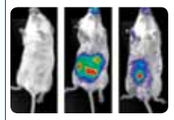
- Department purchased 100 mg of radium for $35,000
- Patient ID on radiographs
- Roll-film apparatus for rapid serial filming

- Synchronous electrocardiography
- Dedicated radiation therapy facility
- Development of NP-59
- Angio & neuro fellowships, later extended to other subspecialties
- MIBG & MIBG therapy
- 1st clinical MR in Michigan 0.35T Diasonics

- Wet laboratory established in MSRB for contrast agent development
- New University Hospital opened

- 1st color Doppler tumor imaging
- Peer review method established; becomes model for national ACR RADPEER system
- MR diffusion & tumor Tx response
- Cancer Center and East Ann Arbor Clinics open
- 1st volumetric image registration
- 1st satellite clinic; Briarwood
- Brighton, Canton and South Main Clinics open
- 1st practical ultrasound blood volume flow measurement
- 1st breast tomosynthesis CAD
- #1 in NIH funding

- 1st photoacoustics of arthritis
- New cyclotron facility (MicroPET) opens in Med Sci I



- Dual energy CT
- Center for Molecular Imaging in BSRB: Animal 7T & 9.4T MR/MicroCT/Bilum
- CMI expands to NCRC
- C.S. Mott Children's Hospital and Von Voigtlander Women's Hospital opened

* News & Information Services, Bentley Historical Library, University of Michigan

RESEARCH SPOTLIGHT

Kilbourn & Scott:
Building the Infrastructure for a Successful PET Program

by Aimee Balfe

WHAT IS IT THAT MAKES THE DEPARTMENT OF RADIOLOGY SUCH A POWERHOUSE IN POSITRON EMISSION TOMOGRAPHY?

Perhaps it's a track record of developing imaging agents for cardiac innervation and neurological diseases now used around the world. It might be the radiochemistry techniques devised here that have become common practice. It could be a research portfolio addressing issues from the early diagnosis of dementia to side effect-free pain management. Or, it may be how we're equipping clinicians with tools to diagnose cancer and quickly assess the course of treatment.

Of course, all these are aspects of the program's success. But how did we get here? Like many success stories, this one involves the right people, the right resources – and perhaps a bit of good luck.

Michael Kilbourn:
Realizing PET's Potential

One of these "right people" is Professor Michael Kilbourn, PhD, who until recently headed the cyclotron facility, which produces the positron-emitting isotopes needed for PET imaging. He ran the department's previous cyclotron for almost 20 years and designed its new, state-of-the-art facility that came online in 2006. In many ways, Kilbourn's leadership of both the facility and the radiochemistry program has underpinned the department's success in PET.

Mentored by two of the early PET leaders at Brookhaven National Laboratory and Washington University, Kilbourn was recruited to U-M in the late '80s. The decision to come was easy, he says, in part because he was a native Michigander and U-M alumnus, and in part because U-M had what he considers a critical contributor to a successful PET program: "marvelous physician-researchers who not only contribute ideas but actually take the radiopharmaceuticals we develop into clinical studies and build a research program of their own."

Upon arriving, Kilbourn launched his own neurologically oriented research program and immediately set about ensuring that the facility under his charge was poised to support the work of colleagues interested in radiopharmaceutical use and development. He augmented the existing cyclotron with the lab infrastructure needed to dramatically expand production.

Perhaps this is where an element of luck kicked in. One of those early researchers whose work he supported was Donald Wieland, PhD, a radiochemist with a focus on cardiology. "A truly unique aspect of U-M, which didn't happen anywhere else that I know of, was that it supported Don and myself – two senior radiochemists who collaborated well and didn't step on each other's toes." One result was the development of carbon-11-labeled hydroxyephedrine ([^{11}C]HED), which is now used around the world for studies of heart innervation.

Of course, the radiochemists in Kilbourn's group were also busy on projects of their own – with equally impressive results. In radiochemistry, they introduced several basic techniques that are now used throughout the field. These include methods for fluorine-18 labeling of aromatic compounds; the development of [^{11}C]methyl triflate, a reagent that expanded the number of molecules that could be quickly labeled with ^{11}C; and the development of a process for simplifying ^{11}C labeling, which they termed "thin-film radiochemistry," but which was commercialized by others as "loop chemistry."

IN RADIOPHARMACEUTICAL DEVELOPMENT, KILBOURN'S GROUP HAS HAD PARTICULAR SUCCESS DEVELOPING AGENTS FOR IMAGING THE LOSS OF NEURONS ASSOCIATED WITH DOPAMINE AND ACETYLCHOLINE, THE HALLMARK OF PARKINSON'S AND ALZHEIMER'S DISEASES.

In radiopharmaceutical development, Kilbourn's group has had particular success developing agents for imaging the loss of neurons associated with dopamine and acetylcholine, the hallmark of Parkinson's and Alzheimer's diseases, respectively.

Part of this achievement he attributes to taking a unique approach to his targets. His work on movement disorders is a prime example. In trying to target proteins specific to dopaminergic neurons, most researchers focused on membrane transporters. Kilbourn's group instead aimed at vesicular transporters. The result was [^{11}C]dihydrotetrabenazine (DTBZ), which is now widely used to study Parkinson's and other neurodegenerative diseases. Kilbourn has since

RESEARCH SPOTLIGHT

collaborated with a researcher at the University of Pennsylvania to develop an ^{18}F-labeled form, which is in clinical trials by Eli Lilly.

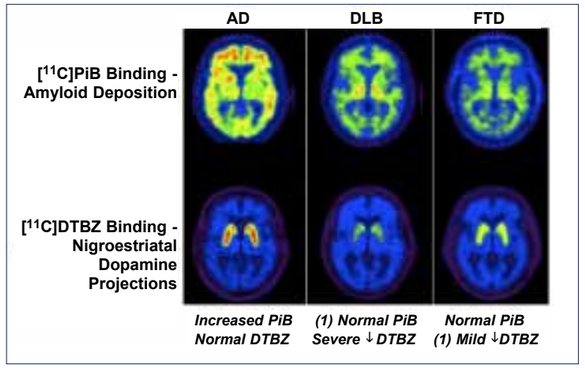
Using a similar approach, his group developed [^{18}F] fluoroethoxybenzovesamicol (FEOBV), a radiotracer targeting the vesicular transporter of acetylcholine, designed for studies of Alzheimer's and related diseases. They've also developed another radiotracer for such studies, [^{11}C]methylpiperidin-4-yl propionate (PMP), which is a substrate for the enzyme acetylcholinesterase.

As a result of this and related work, Kilbourn received the Society of Nuclear Medicine's 2009 Paul C. Aebersold Award for Outstanding Achievements in Basic Science.

But it is not the development of the radiotracers themselves that most excites Kilbourn; it's what researchers can do with them. "One of the major strengths of our research programs is using multi-tracer approaches to understand neurodegenerative diseases," he says. "For example, our neurological research grant doesn't just ask one question; it uses multiple radiotracers targeting multiple neurotransmitter systems all in the same patients. Our study subjects typically get two, three, or four PET scans looking at different aspects of their brain biochemistry. This is critical because most neurological diseases involve more than one transmitter system."

This is possible, he says, because of U-M's cadre of physician-researchers who can devise such studies; a strong image analysis core; and resources like the state-of-the-art cyclotron facility (see p. 14), which allows the use of ^{11}C-labeled imaging agents. Their short 20-minute half-life requires an on-site cyclotron and allows researchers to do two studies in the same subject on the same day—whether with the same radiotracer and a pharmacological or behavioral intervention between, or with two different radiotracers. "Without this facility," says Kilbourn, "there would be virtually no clinical studies involving multiple radiotracers."

A clear example of the value of such studies is a recent collaboration among Kilbourn; Kirk Frey, MD, PhD, chief of nuclear medicine; and Robert Koeppe, PhD, director of medical physics. Their multi-tracer study featuring Kilbourn's signature DTBZ demonstrated the potential of PET imaging to differentiate Alzheimer's disease (AD), dementia of the Lewy bodies (DLB), and frontotemporal dementia (FTD) (see box above).



Kilbourn and his PET colleagues used dual radiotracers, including one he developed, to differentiate Alzheimer's disease (AD), dementia of the Lewy bodies (DLB), and frontotemporal dementia (FTD).

Peter Scott:
Continuing the Momentum

After spending a career building a top-tier facility and track record, the only thing left for Kilbourn was to ensure its sustainability by tapping a strong successor. Last year he handed the reins to his former postdoc, Assistant Professor Peter Scott, PhD, who now serves as director of PET radiochemistry and the cyclotron.

For his part, Scott has hit the ground running. He's already launched a whole new subfield, which he's termed "green radiochemistry." Thanks to his leadership, the facility can now produce more than ten ^{11}C-labeled radiopharmaceuticals using ethanol as the only organic solvent. "We've eliminated the better part of a dozen toxic organic solvents from the lab," he says, "and people are starting to follow our lead."

He is also hoping to add another dimension to his colleagues' work on diagnosing dementia. "We'd like to see if we can use PET imaging to diagnose the disease before a patient is symptomatic and improve diagnostic accuracy," says Scott. "Right now, clinical accuracy using memory tests and such is only about 60 to 80 percent. So there's a 20 to 40 percent chance that a dementia patient will get the wrong diagnosis."

While much of the field has been working to image the amyloid plaques so prevalent in the brains of Alzheimer's patients, Scott, like his mentor, has taken a different approach. He's looking instead at the tau proteins that form the accompanying tangles.

SCOTT HAS HIT THE GROUND RUNNING. HE'S ALREADY LAUNCHED A WHOLE NEW SUBFIELD, WHICH HE'S TERMED "GREEN RADIOCHEMISTRY."

"Unlike amyloid," says Scott, "tau burden actually correlates with cognitive decline. But currently there are no approved radiotracers for imaging tau. So a lot of my work has focused on developing one using a lansoprazole scaffold."

He and his collaborators have also been looking at tau in diseases beyond Alzheimer's. "We're studying it in progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia," Scott says. "We can do this because we have access to brain samples that are positive for all of these from the Michigan Alzheimer's Disease Center Brain Bank." The team is currently evaluating their second-generation radiotracer for imaging tau, which they hope will be ready to move into clinical research next year.

Another area of strong progress is in pain management. Scott and his collaborator, James Woods, PhD, from the Department of Pharmacology, have been looking at compounds targeting the nociceptin receptor, an opioid receptor different from those targeted by traditional painkillers like morphine. Nociceptin agonists had already been shown to have tremendous advantages – they're non-addictive and don't have side effects like respiratory depression. Woods' lab had previously shown that they were effective in pain relief. What was needed was to confirm that Woods' compounds were hitting their intended target. Scott, with the help of a ligand provided by Eli Lilly, was able to conduct receptor occupancy studies using PET to see whether the compounds were indeed reaching the nociceptin receptor. The team hopes this work will usher in what Scott calls "a new horizon in non-addictive pain management."

The Road Ahead

When asked where they're going from here, each has his own perspective. Kilbourn is keen to focus on his research, which includes developing radiotracers for monoamine oxidase/neural inflammation, cathepsin-K/osteoporosis, and GABAA transporter/epilepsy. Naturally, Scott has a broader view. In addition to building his research program, he wants to be sure the university is maximizing the use of its PET resources. "This involves making the best use of the cyclotron and bringing online non-cyclotron-produced radioisotopes like Gallium-68," he says. "We also want to ensure that we're always cultivating collaborations. We have more radiopharmaceuticals in clinical use than probably anyone else in the country. It's a testament to this facility and to the widespread interests of our faculty. We're eager to see that continue."

U-M's State-of-the-Art Cyclotron

Professor Kilbourn designed U-M's current $10 million cyclotron facility in 2005 to meet demand from clinicians and researchers for the radioisotopes required for PET scanning. It was built the following year with support from the NIH and the Department of Radiology. When asked what he's most proud of about the facility, his answer may sound surprising. "It's attractive," he says.

"Of course, we knew we wanted it to be highly functional," Kilbourn continues. "All the equipment had to have good reliability and operational reproducibility. And the facility had to be both expandable and flexible enough to accommodate a changing regulatory environment."

But what strikes visitors is how different it looks from other cyclotron facilities. "Most are cramped, dreary, retrofitted, and tucked somewhere in a basement," he says. "This one has windows to get light into the personal spaces. The offices all have glass walls and high ceilings. And as much as I could, I banned the color gray. It's a pleasant work environment."

It's also remarkably productive and cost-effective. One of its key clinical roles is to provide [^{18}F]fluorodeoxyglucose (FDG), the workhorse of cancer imaging, to the hospital. It does so much more cost-effectively than using a commercial provider, and its output has allowed hospital staff to double their scanning capacity. They now scan some 30 patients a day, and additional patients and scanners can be accommodated simply by running the cyclotron a bit longer.

In addition, the facility produces one of the world's richest arrays of radiopharmaceuticals, all of which are used routinely in patient and animal studies. It also supports collaborations with pharmaceutical companies for preclinical work and clinical trials.

"The goal was to have enough equipment and people to service all these requests," says Kilbourn modestly, "and I think we've been pretty successful."

For more information on U-M's cyclotron, please visit this website.

Continued from page 3

Xueding Wang, PhD. Luker specializes in using bioluminescence imaging and intravital fluorescence microscopy to analyze the signaling pathways regulating tumor growth, metastasis, and drug resistance in cell and animal models of breast cancer. His work has allowed the visualization of ligand-receptor binding and the activity of proteasomes (cellular organelles responsible for degrading proteins), both of which are targets for chemotherapy. His group is making significant progress in analyzing the mechanisms of cancer progression and treatment.

Wang's work focuses on photoacoustic imaging. He is on the cutting edge of this new imaging technique, which processes ultrasound waves generated when laser pulses are applied to biological samples, and allows researchers to evaluate optical information from the tissue to the cellular level. Because it is capable of quantifying physiological biomarkers of cancer, such as oxygenation and pH levels, Wang is using photoacoustics to study prostate cancer and has already built a breast 3D photoacoustic imaging system. He's also using the technique to image inflammatory arthritis and is attaching gold nanoparticles to antirheumatic drugs to visualize their uptake by inflamed joint tissues and study the drugs' efficacy.

Professors Brian Fowlkes, PhD, and Paul Carson, PhD, and their groups are interrogating at the cellular level, as well. By using ultrasound to agitate injected microbubbles in the location of specific cells, their groups target these cells for imaging and for the delivery of what would be toxic concentrations of drugs, hormones, or acoustic energy if administered to the entire body. This has helped them deliver cancer therapies to specific cells and injectable dyes to study drug release, effects, and retention, among other applications.

Carson's group has also made important progress using 3-D automated ultrasound in conjunction with breast tomosynthesis to improve breast cancer detection and assessment. This work complements that of Professor Heang-Ping Chan, PhD, whose focus Dunnick cites as another key future direction: computer-aided diagnosis, or CAD.

"In addition to molecular imaging, CAD is an important future direction for our field," says Dunnick. "Here we've started with breast cancer. The concept involves using computers to analyze various features of a diagnostic image to identify areas that are most likely to be cancer. Radiologists might be able to pick up 70 percent of cancers, but the computer program can increase this sensitivity by flagging areas of concern. Then the radiologist can reexamine those areas to determine whether any require a workup."

Chan's lab has developed an advanced CAD system for detecting microcalcifications, which can be an early sign of cancer, in digital breast tomosynthesis. This adds to her lab's other CAD systems for mammography, as well as lung cancer, pulmonary embolisms, urinary tract cancer, and atherosclerotic plaques in CT and multiple myeloma in MR. Her group not only develops computerized methods of detection but also uses machine learning and quantitative image analysis methods to build decision support systems for risk prediction, diagnosis, and treatment response monitoring. Chan has just been named the Paul L. Carson, PhD, Collegiate Professor of Radiology for her work in this area (see p. 20).

These are just some of the many ways researchers in the department are working to understand the structural and functional aspects of disease so they can make the next 100 years even more transformative than the last.

FACULTY PROFILE

Dr. Kyung Cho: Interventional Radiology at Its Best

by Aimee Balfe

In the world of academic interventional radiology (IR), Professor Kyung Cho, MD, is, as they say, "the total package."

From graduating top of his class in medical school to winning IR's highest honor last year in both the U.S. and his native Korea, he's spent a career as a perfectionist and a leader. He is a procedural virtuoso, known for his precision in even the most advanced techniques. His research has tested now-ubiquitous medical devices and techniques. And he is a committed teacher, beloved by his students not only for his technical training, but for his model of compassion, attention, and patient care.

His career has been filled with remarkable moments – not the least of which is how it started.

A Breech Baby Launches a Career

"I went to medical school in Korea," says Cho, "and was drafted the moment I graduated. It was 1966, and I was the doctor assigned to an air force base on a small island off the coast of North Korea. But this was before doing an internship, so I had no clinical experience. Soon I found myself having to deliver a baby, which I'd never seen done – and it was breech. The baby eventually came out, but the placenta didn't – so the patient continued to bleed. I had to transfuse her with a unit of my own blood so she could be transferred to Seoul. Both she and the baby made it, but that experience drove me to look for more innovative ways to rescue such patients."

Cho found the field that would ultimately answer this call after completing his military service and coming to the U.S. to finish his education. After an internship and residency in Detroit, he took a fellowship at U-M in the burgeoning field of angiography. Such was his skill and work ethic that upon completing his fellowship, he was named chief of angiography at Wayne County General Hospital. Within a year, he'd become director of interventional radiology at U-M.

His location and timing were perfect. It was the early 1970s, and angiography was expanding into an interventional field. In the '50s, angiographers were using needles, guidewires, and catheters, to visualize blood vessels. By the '60s, narrowed vessels were being dilated with angioplasty. "Then at U-M in the '70s," says Cho, "Dr. Joseph Bookstein and Dr. Stewart Reuter introduced embolization to control bleeding in the GI tract and kidneys. They paved the way for U-M's world-class program in IR."

Procedural Firsts

By the '80s, Cho was becoming something of a pioneer himself. One of his more ground-breaking cases involved a newborn who was referred to him with a pelvic hemangioma the size of a small football. The affected vessel was shunting blood so quickly the baby's heart was failing. "The only surgical option was to remove part of her pelvis, and that was unthinkable," says Cho. "But I was able to thread a catheter through her umbilical artery and embolize the lesion. It was the first time this condition was treated with IR and my first time using IR to save a life."

A year later, Cho had another first: an 11-year-old boy with severe hypertension brought on by a narrowed artery in his kidney. The narrowing reduced blood flow to a small portion of the kidney, which in turn released the hormone renin, causing the boy's blood pressure to spike. Surgery hadn't worked, so Cho used a catheter to reach the narrowed region and a small amount of ethyl alcohol to cut off blood flow to the area. It was the first case of using IR to cure hypertension in a child.

Foundational Research

Around this time, Cho took a sabbatical to work with the world-renowned interventional radiologist Anders Lunderquist in Sweden. Their research on hepatic microcirculation provided important structural insights that brought microcirculation to the attention of angiographers and helped physicians better understand complications related to liver transplants and cancer treatment.

"I WAS FORTUNATE TO BE ABLE TO WORK WITH WORLD LEADERS IN THE FIELD AND LEARN THE MOST INNOVATIVE TECHNIQUES."

Upon his return, Cho collaborated with Surgery Chair Lazar Greenfield, MD, to assess competing designs for vena cava filters, used to protect patients from life-threatening pulmonary embolisms. Their results confirmed the superiority of the conical design, and provided an evidence-based guide for selecting safe, effective filters among the dozen or so on the market.

Most recently, Cho has concentrated on carbon dioxide (CO_2) as an angiography contrast agent. He's shown that when used properly, it's safer than its iodinated counterparts, which cause allergic reactions and can damage the kidneys. He's written the first textbook on CO_2 angiography, and has been traveling the world promoting CO_2 and educating angiographers on its advantages, use, and contraindications.

Paying It Forward Through Teaching

Looking back on his career, Cho rattles off a long list of mentors of whom he speaks with deep appreciation. He's made it a theme of his career to do for others what his mentors did for him.

"I was fortunate to be able to work with world leaders in the field and learn the most innovative techniques," says Cho. "I would practice them in the lab, see how effective and safe they were in animals, and then apply them to patients."

He's used the same model in his teaching. His students watch his technique, practice repeatedly in the lab, and only then treat patients under his watchful eye.

He does this not only with his fellows but in his renowned short course, "Practical Training in Vascular Interventions," which he developed to ensure that physicians from other disciplines who were using IR techniques were truly mastering them. "Our goal is to give vascular surgeons, interventional cardiologists, and others the type of training we provide in an IR fellowship, but condensed into five days," he says.

The course is a manifestation of Cho's deep commitment to patient care. "As our field has perfected these minimally invasive techniques, patients have come

FACULTY PROFILE

to demand them," he says. "So now interventionalists from other specialties are using our equipment and learning to use the wire and catheter without in-depth training or often the best technique. My goal was to help patients by bringing interventionalists to U-M and training them well, so we can minimize complications."

But Cho, who for years directed the vascular and IR fellowship programs, didn't earn U-M's Lifetime Achievement Award in Medical Education for just perfecting his trainees' technique. He tries as much as possible to model the type of physician he wants them to be. "I come to work early to do rounds, and I stay late at night," he says. "I try to be very enthusiastic and to give my trainees as much time as possible. I never tell them I'm too busy. And I try to teach core values – respect, compassion, collaboration, innovation, and commitment to excellence."

Still on Top

It is these values that in 2012 made Cho one of only about 40 physicians ever to be awarded the U.S. Society of Interventional Radiology's Gold Medal. He won it the same year in Korea.

He has used this platform to advocate for the future of the field, where he is concerned about the migration of cases to other specialties, leaving only the most complicated for IR. He's urged his colleagues to view themselves not as proceduralists but as providers of comprehensive care. He's encouraged universities and hospitals to better support his subspecialty. And he's called for educational campaigns, both among patients who are often unfamiliar with the field and among primary care physicians who provide the referrals.

He's passionate about the field's future because, he says, he's still awed by the miracles it can perform. The biggest of his career happened just recently as he was placing the first of a few coils in a patient's vessel to stop a complex, life-threatening hemorrhage. Before he could finish, the patient arrested and, after extensive CPR, was pronounced dead. While Cho was sitting downcast in his office, his fellow rushed in to say the coil had done its job and the patient had actually come back to life.

These are the moments he's lived for — and equipped generations of interventionalists to experience, as well.

Dr. Cho is the William Martel Collegiate Professor of Radiology and currently directs the radiology animal imaging lab.

"I TRY TO BE VERY ENTHUSIASTIC AND TO GIVE MY TRAINEES AS MUCH TIME AS POSSIBLE. I NEVER TELL THEM I'M TOO BUSY. AND I TRY TO TEACH CORE VALUES – RESPECT, COMPASSION, COLLABORATION, INNOVATION, AND COMMITMENT TO EXCELLENCE."

Carbon dioxide (CO_2) abdominal aortogram in an elderly patient with renal failure and hypertension. Image credit: Kyung Cho, MD.

FACULTY AWARDS + RECOGNITION

Prachi Agarwal - Young Investigator Scholarship from the World Congress of Thoracic Imaging

Richard Brown - Associate Editor, Radiographics

Ronald Bude - Associate Editor, Radiology

Ruth Carlos - Deputy Editor, Journal of the American College of Radiology

Paul Carson - William Fry Memorial Lecture, American Institute of Ultrasound in Medicine

Kyung Cho - Gold Medal from the Korean Society of Interventional Radiology

Richard Cohan - Associate Editor, Radiology

Michael DiPietro - Lifetime Achievement Award for Clinical Care, University of Michigan Dean's Award

N. Reed Dunnick - Gold Medal, Michigan Radiological Society; Honorary Member, Japan Radiological Society; Innovation and Leadership Award, Radiology Research Alliance

Brian Fowlkes - Kennedy Team Research Award from the College of Engineering, University of Michigan

Jon Jacobson - Assistant Editor, American Journal of Roentgenology; Honored Educator Award, Radiological Society of North America; Magna Cum Laude Award for Scientific Exhibit, Radiological Society of North America

Kate Klein - Gender Equity Award from the American Medical Women's Association

Gary Luker - New Investigatory Award from the Radiology Research Alliance

Kate Maturen - GERRAF Award ($150,000) from the Association of University Radiologists

Venkatesh Murthy - The Young Investigator Award from the American Society of Nuclear Cardiology

Douglas Quint - The University of Michigan Dean's Outstanding Clinician Award; Friend of Neurosurgery Teaching Award

Wael Saad - Assistant Editor, American Journal of Roentgenology

Ashok Srinivasan - Associate Editor of Radiology

Robert Welsh - Distinguished Reviewer, Journal of Magnetic Resonance in Medicine

"Best Doctors in America" - 35 radiology faculty were named in 2012-13

Academy of Radiology Research Distinguished Investigator Award - 12 Michigan Faculty were named (Tied with Johns Hopkins and Stanford for most faculty)

In January 2013, the following faculty from the Department of Radiology were inaugurated into the Medical School's League of Educational Excellence:

Kyung Cho, MD
Richard Cohan, MD
Michale DiPietro, MD
Jon Jacobson, MD
Peter Liu, MD
Douglas Quint, MD
James Sisson, MD

The following faculty were promoted in 2013. CONGRATULATIONS!

Mahmoud Al-Hawary, MD – Clinical Associate Professor

Qian Dong, MD - Clinical Associate Professor

Lubomir Hadjiyski, PhD – Research Professor

Mohanned Ibrahim, MD – Clinical Associate Professor

William Weadock, MD – Clinical Professor

Robert Welsh, PhD – Research Associate Professor

PROFESSORSHIPS

INAUGURATION OF THE PAUL L. CARSON, PHD, COLLEGIATE PROFESSORSHIP IN RADIOLOGY

HEANG-PING CHAN, PHD, RECIPIENT

(left to right) - N. Reed Dunnick, MD (Radiology chair), Paul Carson, PhD (donor), Heang-Ping Chan, PhD (recipient), James Woolliscroft, MD (Dean, Medical School).

On May 30, 2013, Heang-Ping Chan, PhD, was inaugurated as a Carson Professor. After earning her undergraduate degree in physics and mathematics from the Chinese University of Hong Kong in 1974, Dr. Chan received her doctorate in medical physics from the University of Chicago in 1981. She joined the Department of Radiology at the University of Michigan as associate professor of radiology in 1989 and has been a professor of radiology since 1995. As the director of the Computer-Aided Diagnosis Research Laboratory in the Department of Radiology, Chan's recent research includes the investigation of stereomammography, the development of computer-aided diagnosis systems for breast cancer in mammography, ultrasonography and digital breast tomosynthesis, development of computer-aided diagnosis systems for lung cancer in computed tomography (CT), and analysis of breast parenchymal pattern for cancer risk prediction.

Her current NIH-supported research, totaling more than $4 million, focuses on computer-aided detection of non-calcified plaques in coronary CT angiograms, microcalcification detection in digital breast tomosynthesis and study of digital breast tomosynthesis imaging and reconstruction techniques.

She also collaborates with colleagues on other projects including combined breast tomosynthesis, optical and ultrasound imaging, computer-aided detection of pulmonary embolism on CT pulmonary angiography, computer-aided diagnosis of urinary tract cancer on MDCT urography, development of image biomarker for treatment response assessment of head and neck cancer, and development of image biomarker for treatment response assessment of multiple myeloma. Chan has authored or coauthored more than 170 peer-reviewed journal articles, as well as more than 400 presentations for international conferences. Chan became a fellow of the American Association of Physicists in Medicine and a fellow of the Institute of Physics in 2004, and was named a Distinguished Investigator of the Academy of Radiology Research in 2012.

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INAUGURATION OF THE ROGER A. BERG, MD, RADIOLOGY RESEARCH PROFESSORSHIP

BRIAN D. ROSS, PHD, RECIPIENT

A national leader in molecular imaging—one of the major frontiers of radiology research—Brian D. Ross, PhD, was installed as the first Roger A. Berg, MD, Radiology Research Professor on October, 26, 2012.

Dr. Ross earned his doctorate in biophysics in 1987 from the University of California, Davis. He completed a fellowship in 1990 at the University of Minnesota and was appointed in 1996 as an assistant professor at the University of Michigan. He rose through the ranks to professor in the departments of Radiology and Biological Chemistry.

His research has made great progress in helping to interrogate cellular signaling pathways using imaging and development of imaging biomarkers capable of predicting whether or not a tumor will be responsive to a given method of treatment early in the course of treatment, rather than waiting months to detect gross changes.

Ross has enjoyed great success in mentoring junior faculty who have gone on to become successful independent investigators. He has been honored with the Outstanding Teacher Award by the International Society of Magnetic Resonance in Medicine and recently was installed as a fellow of the society for significant and substantial contributions to research.

He has an excellent record of service in the field as a founding member of the Society of Molecular Imaging, serving as its president in 2005. He also is founding editor of the internationally recognized oncology journal Neoplasia. He co-authored the definitive textbook in his field, "Molecular Imaging: Principles and Practice," and has published extensively with 165 citations.

Click Here To Give

(left to right) - Brian Ross, PhD (recipient), Roger A. Berg, MD (donor) and N. Reed Dunnick, MD (Radiology chair).

professorships

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