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Quo Vadis Pediatric Nuclear Medicine

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What has happened to the nuclear medicine subspecialty since those earlier issues of the *Seminars in Nuclear Medicine*? The earliest issues in 1972 presented topics in vogue at the time that included brain "scanning," cisternography, whole body counting, and abdominal imaging with ^{99m}Tc pertechnetate. The second pediatric subspecialty issues in 1993 reflected a 21-year evolution of the subspecialty and included the topics of renal scintigraphy, labeled cells for abdominal imaging, metaiodobenzylguanidine imaging, single photon emission computed tomography, and bone scintigraphy for benign disorders. The current issues will address diverse topics that cover the spectrum of the current practice of pediatric nuclear medicine. They include radiation exposure and absorbed dose reduction, positron emission tomography/computed tomography in children, neuroblastoma and other neuroendocrine tumors, thyroid cancer and therapy, bone density studies and, of course, the most prevalent studies in children, renal and bone. Brain, heart, and lung studies complete the spectrum.

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This issue and the next issue of the *Seminars in Nuclear Medicine* join the previous issues of the *Seminars* that are dedicated to the topic of pediatric nuclear medicine (PNM). What has happened to the nuclear medicine subspecialty since those earlier issues of the *Seminars*? The earliest issues in 1972 presented topics in vogue at the time that included brain "scanning," cisternography, whole body counting, and abdominal imaging with ^{99m}Tc pertechnetate.^{1,2} The second pediatric subspecialty issues in 1993 reflected a 21-year evolution of the subspecialty and included the topics of renal scintigraphy, labeled cells for abdominal imaging, metaiodobenzylguanidine (MIBG) imaging, single photon emission computed tomography (SPECT), and bone scintigraphy for benign disorders.^{3,4}

The current issues will address diverse topics that cover the spectrum of the current practice of PNM.^{5,6} They include radiation exposure and absorbed dose reduction, positron emission tomography/computed tomography (PET/CT) in children, neuroblastoma and other neuroendocrine tumors, thyroid cancer and therapy, bone density studies and, of course, the most prevalent studies in children, renal and bone. Brain, heart, and lung studies complete the spectrum.

Predicting the future is a difficult task at best. In medicine, significant advances occur primarily through research and occasionally through serendipitous observations, ie, the

search for a rapid diagnosis for appendicitis led to the recognition of ectopic gastric mucosa in Meckel's scintigraphy.⁷ The most recent prediction for the future of PNM proposes a combination of PET/CT along with radionuclide therapy as the most significant future trends.⁸ PET/CT has proven of significant value in the diagnosis and management of adult and childhood oncology disorders and has stimulated a recent growth spurt in the usage of PET/CT. However, oncology disorders in childhood have a much lower incidence than benign and genetic disorders. Can one rely on the low incidence of oncology disorders in childhood with its subsequent small economic return to portend a future significant growth of PNM?

It may be of interest to speculate on the future of PNM by reviewing those factors that impacted on its usage during the previous four decades. With this concept in mind, I petitioned practitioners of nuclear medicine via the PNM website⁹ for their most recent 2005 examination data. There were 10 responses primarily from major pediatric centers throughout the world, including Australia, Canada, Europe, the United Kingdom, and the United States (Table 1). The data from each institution were rounded off to determine the gross percentages of usage. Types of studies were grouped together under one category, ie, a renal category that included radionuclide cystography, renography, renal scintigraphy, and glomerular filtration rate. The method of determining what procedure or procedures constituted an individual study was not determined from the raw data provided from each institution. The number of studies that were performed in each institution ranges from 394 to 5,719 studies per year. An

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Table 1 Pediatric Nuclear Medicine 2005

	Brussels	Chicago	Sidney	Vancouver	Munich	Cincinnati	Paris	Boston	UK 1	UK 2
Exams	1,300	1,303	2,259	3,800	394	4,013	2,409	5,719	1,805	2,340
Renal	50%	49%	43%	37%	57%	57%	29%	53%	90%	74%
Bone	20%	19%	22%	20%	6%	17%	44%	18%	4%	8%
Tumor-brain	5%	12%	15%	22%	24%	11%	7%	11%	3%	10%
GI	15%	15%	14%	17%	13%	8%	0%	6%	2%	3%
Heart-lung	10%	2%	6%	4%	0%	4%	20%	11%	1%	5%

approximate total of 25,500 studies were performed in the 10 hospitals.

The Past

Many of the earliest specialist practitioners of PNM had a background in radiology. Because little or no training was available in the application of nuclear medicine in the pediatric population, they learned on the job and indeed created many of the techniques that were developed and are still in vogue today. Perhaps, because of their radiology background, they were impressed by the unique method of obtaining anatomic images with radiopharmaceuticals. As a consequence, the initial view of many was to envision nuclear medicine as a means of anatomically depicting organs such as the brain and thyroid gland that were difficult to visualize with routine radiograph techniques. Another major incentive for the early use of nuclear medicine in children was its noninvasive character, especially when compared with the invasive catheter techniques that were developing in pediatric radiology during the 1960s.

Despite this, the use of nuclear medicine in children was slow to progress. The commercially available radioisotopes in the 1960s, ie, ^{131}I and ^{203}Hg , were less well suited for use in pediatrics because of their high energies and long biological half-lives. In addition, rectilinear scanners were slow and produced less than optimal images.

A further impediment for the use of radioisotopes in children was government regulation.¹⁰ After World War II, the use of radioisotopes for medical purposes in the United States was controlled by the Atomic Energy Commission (AEC). After the Food and Drug Administration (FDA) took over the responsibility for radioisotope approval, the FDA approved a number of radiopharmaceuticals that were commonly used in adults from a so-called "well-established list." However, the FDA also adopted the policy of requiring controlled clinical trials to determine the "safety and efficacy" of the "well-established list" radiopharmaceuticals for use in children.

Because of the limited volume of studies that were being performed in children, radiopharmaceutical manufacturers were reluctant to conduct the costly clinical trials required for FDA approval, and PNM lingered more or less as a regulatory orphan in the rapidly developing field of nuclear medicine. The "Orphan Clause" that stated the radiopharmaceutical had not been tested for "safety and efficacy" in children implied that the practitioner using that radiopharmaceutical did so at his or her own volition and risk on an individual pre-

scription basis. The FDA-approved radiopharmaceutical package inserts with an appended "orphan clause" were a considerable deterrent to the growth of PNM in the early 1970s. Several PNM practitioners, with the cooperation of their institutions and the FDA, conducted limited clinical trials that enabled the FDA approval of the most commonly used radiopharmaceuticals in children and the subsequent decreased use of the "orphan clause" in package inserts.¹¹ In recent years, new radiopharmaceuticals with promising usefulness in children have undergone manufacturer controlled clinical trials.¹²

A major impetus for the early growth of PNM occurred with the development of the gamma camera by Hal Anger.¹³ The first commercially available Gamma Camera installed in a pediatric center was at the Chicago Children's Memorial Hospital in the Summer of 1967 (Fig. 1).¹⁴ That 19 phototube Gamma scintillation camera, the Pho Gamma III, became commercially available from the Nuclear-Chicago Corporation in Des Plaines, Illinois.

Another major stimulus for the growth of PNM was the commercial introduction of $^{99\text{m}}\text{Tc}$ radiopharmaceuticals.¹⁵ In the 1970s, brain scintigraphy with $^{99\text{m}}\text{Tc}$ pertechnetate became a predominate study. The rapid diagnosis of brain tumors and nononcology brain disorders such as subdural collections and congenital malformations such as the Dandy-Walker cyst rapidly replaced the more invasive radiograph studies such as pneumoencephalography. Other organ disorders that were difficult to diagnose with routine radiograph techniques, such as the recognition of pyelonephritis and renal transplant rejection, soon became popular studies for nuclear medicine.

In the mid 1970s, computed tomography (CT) was introduced into clinical practice. Although early CT instrumentation and images were primitive, the technique was an obvious significant advancement in the anatomic diagnosis of adult and pediatric disorders, especially for the brain. As a consequence, brain scintigraphy experienced an immediate decrease in its use.¹⁴ Referring practitioners recognized the lesser ability of nuclear medicine to diagnose disorders based on anatomic imaging and, thus, practitioners turned to nuclear medicine's forte, that is, functional imaging at a molecular level. Renography, renal transplantation scintigraphy, and radionuclide cystography replaced brain scintigraphy as the bread winners for PNM and remains so even to this day. Approximately 53% of PNM studies today are in the renal category. The introduction of $^{99\text{m}}\text{Tc}$ phosphate radiopharmaceuticals¹⁶ further opened the doors for the study of benign

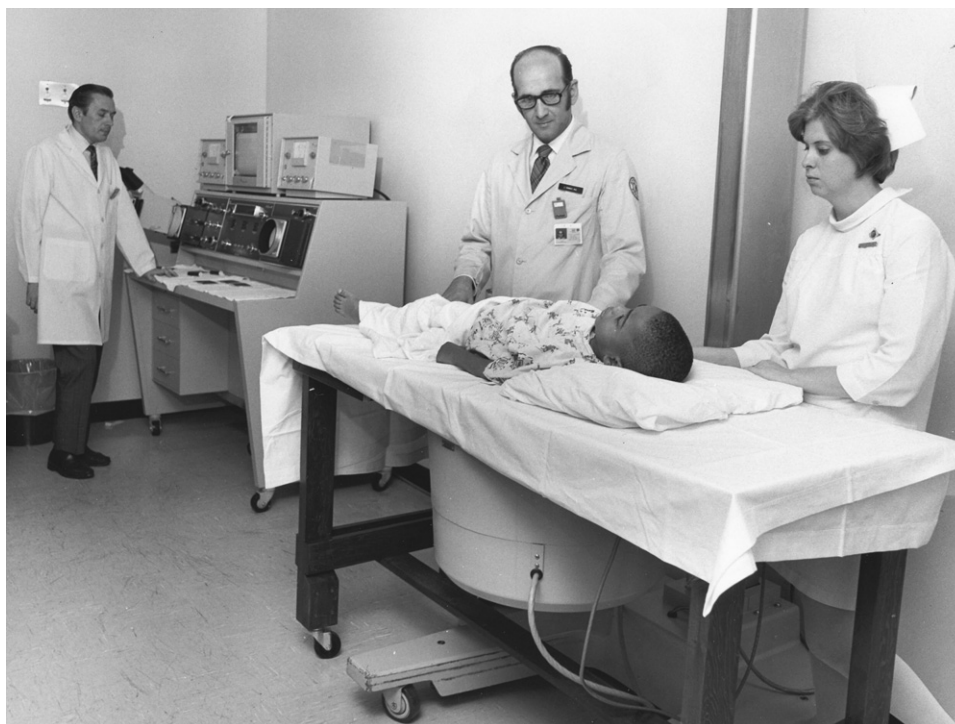


Figure 1 First Anger gamma camera to be installed in a pediatric hospital at the Children's Memorial Hospital in Chicago, Illinois, in 1967. The 19 phototube gamma camera from Nuclear-Chicago Corporation was further equipped in 1969 with dual-rate meters and a graphic chart recorder. By using another camera technical improvement, ie, "the split crystal" technique, individual renogram graphs for each kidney could be derived. Such early studies often were accompanied by a nurse in attendance. Note the handmade table with a cutout that allowed the child to lie directly on the collimator face for the best resolution. Mr. Vincent Czakowski was an early pediatric nuclear medicine technologist that assisted in developing techniques for pediatric studies. Sue Weiss, CNMT, and James Everett, CNMT, also were essential contributors in the early development of pediatric nuclear medicine techniques at the Children's Memorial Hospital of Chicago.

and nononcology orthopedic conditions and the growth spurt in PNM continued. Approximately 19% of PNM studies today are in the bone category. Renal and bone, therefore, account for almost three-fourths of our workload today, and the vast majority of that workload is for nononcology disorders.

A review of the influences that, in my experience, impeded or stimulated the growth of PNM during the last 40 years results in the following considerations that may be applied to predict the future for PNM. The major factor impeding the growth of PNM has been the introduction of competing imaging technologies such as CT, ultrasound (US), and magnetic resonance imaging (MRI). One might consider that CT may have reached its zenith in anatomic diagnosis even with high-resolution 64-slice technology. Furthermore, PNM practitioners have ceased to compete on an anatomic basis and further improvements in CT will probably have little further impact on PNM. Another important limiting factor for CT's further influence on PNM has been the absorbed radiation dose from high-resolution techniques, especially in pediatric use. The combination of PET/CT imaging has gradually become a popular diagnostic tool in adults and also in children and has stimulated the manufacture and sale of newer instrumentation and fusion software especially for on-

cology imaging. In fact, 93% of the current patient studies performed on PET or PET/CT scanners are for oncology indications and 7% are for cardiac and neurology indications.¹⁷ For pediatric use, only 10% are for oncology disorders and, when combined with heart and neurology disorders, are only 15% in children contrasted with the 100% in adult practice.

Other factors, including the absorbed radiation dose from the combined techniques and, perhaps more importantly, the lower incidence of oncology pathology in children, creates a significant economic impediment for a major financial investment for the pediatric population. Yet, one cannot deny the value of such a diagnostic and management capability for children with oncology disorders. The concern about absorbed radiation dose is of lesser importance when considering the risk versus benefits in children with oncology disorders. However, the use of PET/CT should be of greater concern when considering the risk versus benefits in children with nononcology or benign disorders.

The Present

In analyzing the admittedly limited character of the 2005 usage data from the 10 hospitals (Table 1), it is interesting to note that the usage within the various study categories is

somewhat similar throughout the world, particularly in the larger hospitals. In comparing the data from those 10 hospitals from 2005 with our own data from the mid 1980s into the late 1990s, the percentage of category usages has remained similar. In other words, PNM is currently stable. The introduction of new oncology radiopharmaceuticals such as metaiodobenzylguanadine and octreotid in that interval has not had a great impact on the overall growth of PNM.

Of the approximately 25,500 studies performed at the 10 pediatric hospitals, approximately 90% of the studies were for nononcology disorders. An important consideration, therefore, is that the study of nononcology or benign disorders carries the most weight for an economic return on investment especially for the smaller or specialty pediatric hospitals.

Another factor to be considered is the development of specialist "expertise" in the subspecialty of PNM. Beginning in the 1980s and continuing even today, the concept of "centers of excellence" in hospitals was a driving force for acquisition not only of equipment but also for the acquisition of specialty trained practitioners not only in nuclear medicine but in other pediatric specialties as well.

The "centers of excellence" concept became a strong business marketing force, especially for competition between hospitals within a city or region. It is my belief that the larger pediatric institutions strived to offer subspecialty services for specific pediatric disorders to benefit from the "centers of excellence" marketing. Examples include renal transplantation, cardiac disorders, cystic fibrosis and asthma, genetic, orthopedic, and oncology disorders. The impact of such personnel acquisition significantly influenced the growth of PNM. For example, it is my personal observation that whenever a pediatric urologist was added to our staff, the volume in renal studies would increase by 15%. Another important influence on study volumes are the protocols that are created for research studies especially in oncology. An increase and conversely, a sudden decrease in the number of studies that accompanied a protocol change would affect the utilization of equipment and personnel.

The 1980s "centers of excellence" concept also led to an incentive for the "isolation" of imaging specialists in the larger-staffed pediatric hospitals. A specialist practitioner assigned solely to nuclear medicine excluded his or her acquiring skills in the other developing technologies such as MRI. The subspecialty practitioners of nuclear medicine often thrived in that environment, but the competition to promote which study was best for a given disorder perhaps led to a biased promotion for a specific technology and perhaps overuse of imaging studies. Many smaller-staffed pediatric hospitals could not economically support the subspecialization concept and, as a consequence, their practitioners became more versatile in all aspects of imaging technology, including nuclear medicine.

The Future

It is obvious that the greatest influence on the previous increased use of nuclear medicine in the pediatric popu-

lation has been through the development of new radiopharmaceuticals, especially for the management of nononcology disorders, witness the data for bone and renal studies that make up approximately 72% of PNM examinations.

Therefore, we should ask the question, what different nononcology disorders can benefit from nuclear medicine studies? Although "The Decade of the Brain" has come and gone, it never had an impact on the pediatric world. Nuclear medicine research studies have yielded significant insight into drug addiction and neurological disorders such as dementia in all its forms in adults but less so for pediatric disorders. Our future research into "molecular imaging" perhaps, should emphasize pediatric brain disorders as well. An example might be autism. There are currently estimated to be 150,000 children afflicted with the spectrum of the disorder that falls within the realm of autism. The disorder seemingly is increasing in the pediatric population and, recently, a genetic link has been recognized. The diagnosis of autism is uncommonly made before 2 or 3 years of age, and it is believed that early treatment is beneficial in the final outcome and management of this perplexing disorder. Can we direct our research efforts in so called "molecular imaging" to develop newer radiopharmaceuticals to make an earlier diagnosis in autistic children?

Ultrasound and CT have possibly reached their zenith of capability in anatomic diagnosis. Attempts to devise "functional" imaging with US have had limited success. The molecular nature of nuclear medicine remains its strongest basis for functional imaging. Thus one can predict that the two technologies, US and CT, will probably not substantially impact further on the future growth of PNM.

MRI, on the other hand, continues to develop its potential as a functional imaging technology. A news item on the front page of *The Sunday Chicago Tribune* on December 31, 2006, reported on the potential use of extremely high magnetic fields in MRI that is of great interest. The current clinically available MRI instrumentation monitors activities at a molecular level, ie, the presence of water. The research MRI device developed at the Hospital of the University of Illinois in Chicago, Illinois, uses a 9.3-T magnetic field. It allows recognition of the migration of elemental atoms such as sodium across the cellular membranes of the neuron to excite electrical impulses that transit along the neuronal axon to communicate with adjacent neurons. The potential to investigate brain processes such as thoughts, ideas or decisions is there. Perhaps, we should refer to "elemental imaging" rather than "molecular imaging."

However, MRI has its limitations for such studies in children because of the need for significant sedation especially in younger children. It is also a costly procedure with expensive equipment acquisition costs. MRI research into functional renal imaging has also produced interesting results but again the practicality of applying such studies as a routine procedure in the pediatric population and in the general pediatric hospital setting is limited.



Figure 2 A major contribution to the growth of pediatric nuclear medicine has been the pediatric internet site created by Mike Gelfand, MD, at the Cincinnati Children's Hospital in Ohio. It has brought together practitioners from all over the world. An outgrowth of that interaction was the first "Pediatric Nuclear Medicine College Bowl" at the World Federation of Nuclear Medicine and Biology meeting in Sidney, Australia, in October, 1994. The result of the "Pediatric Challenge Bowl" was a virtual tie among the participants, although the North American team was declared the winner because Gerry Mandel was too quick on the response button with the correct answer. The audience did just as well. The North American team from left to right are Massoud Madj of Washington, DC, Gerald Mandel now of Phoenix, Arizona, Helen Nadel of Vancouver, BC, Canada, Mike Gelfand of Cincinnati, Ohio, and John Miller, formerly of Los Angeles, California. A number of pediatric practitioners are in the audience. (Color version of figure is available online.)

Predictions

A major factor limiting the future growth of PNM is the paucity of training facilities and personnel interested in the pursuit of PNM as a career. Many of the earlier "pioneers" in PNM have retired or are retiring from practice. As in all subspecialty practices, besides a personal interest in a given

specialty, economics will influence the personal decisions for seeking advanced subspecialty training. I believe that the decreasing personpower in PNM will eventually create a demand for appropriately trained practitioners. As a need for well-trained practitioners arises, the increased interest of future practitioners will spark the advent of more training programs. The Department of Nuclear Medicine at the Chil-



Figure 3 The European team from left to right are Rune Sixt of Göteborg, Sweden, Klaus Hahn of Munich, Germany, Amy Piepsz of Brussels, Belgium, and Isky Gordon of London, UK. (Color version of figure is available online.)

Figure 4 The Australian team members are Monica Rossleigh of Sydney, Australia, Robert Howman-Giles of Sydney, Australia, Shane Maroney of South Australia, now of New South Wales, Australia, and Geoff Bower of Western Australia. (Color version of figure is available online.)



dren's Hospital of Boston under the direction of Ted Treves, MD, is an example where a pediatric program in molecular imaging research is now offered.

An important contributor to the continuing success of PNM is the pediatric internet site that currently has more than 275 subscribers throughout the world. It is an important teaching tool for those with perplexing study issues and difficult cases. Techniques for studies, reference sources for the diagnosis of specific disorders and examples of interesting cases are readily forthcoming from practitioners throughout the world. Furthermore, the Pediatric Council of the Society of Nuclear Medicine and the Pediatric Task Group of the European Association of Nuclear Medicine will continue to contribute to the well being of PNM. The network of PNM practitioners that intellectually and socially interact at scientific meetings (Figs. 2-5), on the internet, and on a personal basis has created a worldwide environment that has and will continue to significantly support the growth of PNM.

Quo vadis pediatric nuclear medicine? So, what is the future for PNM? Predicting the future is a difficult task at best. Your guess is as good as mine. I will base my speculation on my experiences during the last 40 years. We are currently in a "holding" pattern. Newer instrumentation in CT and US will probably have a limited influence on the future growth of PNM. Perhaps a combination of PET/MRI and fusion imaging will prove a near term stimulus. Trainees will require significant familiarity with both technologies. The development and proof of value from a PET/MRI study for benign disorders will be required to significantly contribute to the growth of PNM.

I believe that the primary stimulation for the future growth of PNM will be the development of new radiopharmaceuticals to study the different benign disorders of childhood. New radiopharmaceuticals with "molecular imaging" potential to study "benign" pediatric disorders in a functional manner will stimulate its growth and continuing contribution to the well being of the pediatric population.



Figure 5 A pediatric nuclear medicine symposium in Munich, Germany, followed the 1998 World Federation of Nuclear Medicine and Biology meeting in Berlin, Germany. The organizers and speakers of the post congress meeting enjoyed a boat cruise on Lake Starnberg. From left to right: Gerry Mandell, Isky Gordon, Rune Sixt, Mike Mann, Amy Piepsz, Helen Nadel, Michael Gelfand, Sybille Fischer, Pierre Olivier, Monica Rossleigh, Jim Conway, Cees Hofnagel, Sitting is the post congress pediatric nuclear medicine symposium organizer, Klaus Hahn. (Color version of figure is available online.)

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