

# A Memoir of Pediatric Nuclear Medicine: Part 1. Pioneers and Early Advances

**D**r. Conrad Nagle, Newsline editor, has requested that I provide an essay on the history of pediatric nuclear medicine. I recognize that the development of a complex medical discipline results from a series of introductory innovations and contributions by many individual practitioners and by industry. These innovations and contributions, small and large, evolve over time and build one upon the other. Any attempt to define notable events may overlook earlier works or contributions that preceded it. Therefore, I have decided to include both seminal events and a personal memoir of my years in practice.

A memoir is a report or record of events based on the writer's personal observation or special knowledge. It is often corrupted by personal bias and a paucity of knowledge of the true facts surrounding the events. However, without embarking upon a major research project, the memoir can often provide insight into the history of a discipline. The significant events included in this memoir are those that most affected my practice. It is important to remember that it is the popularization of procedures or techniques by individuals that is most easily recalled, not necessarily the first report or original innovator.

## From the Newsline Editor:

James J. Conway, MD, a distinguished pioneer in pediatric nuclear medicine and past president of the SNM, agreed to share with Newsline a retrospective on the development of the subspecialty, including landmark events and discoveries. In Part 1, he outlines some of the early advances and the individuals whose work contributed to bringing pediatric applications into the mainstream of nuclear medicine practice. In installments to appear in Newsline in the coming months, Dr. Conway will discuss the genesis of the Pediatric Nuclear Medicine Club/Pediatric Council and challenges faced by pediatric nuclear medicine in its developing years, including early regulatory efforts. In a final contribution in the series, he will provide a fascinating and highly personal memoir of his own experiences as a researcher, clinician, and educator.

Conrad Nagle, MD

## The Beginnings

In 1946, notable military men and scientists, including H.H. Arnold, Albert Einstein, Harold Urey, and J.R. Oppenheimer, published a booklet titled *One World or None* (1). They were concerned about the future uses of atomic energy and spoke up for applications outside of the military. To my knowledge the first postwar symposium on the use of radioisotopes in biology and medicine was presented at the University of Wisconsin in 1948 (2). Among the nuclear medicine pioneers participating in that symposium were Paul C. Aebersold, MD, Glenn T. Seaborg, PhD, and Joseph G. Hamilton, MD (Fig. 1).

Pediatric nuclear medicine had its clinical beginnings in 1946. According to a Nuclear Regulatory Commission report, more than 1,000 radioisotope studies of the thyroid gland in children and adolescents were performed at 21 institutions in the United States between 1946 and 1948 (3). Thus, early on, many practitioners identified the utility of nuclear medicine in children. Among these researchers was Hamilton at the University of California, Berkeley, who studied the thyroid gland of a child using  $^{131}\text{I}$  and a Geiger-Muller tube. This image of a child undergoing a thyroid radioisotope study has been reproduced many times in texts and presentations as an early example not only of the use of radioisotopes in children but of the introduction of clinical nuclear medicine (Fig. 2).

The development of pediatric applications was hindered over the next decade by the fact that commercially available radioisotopes and imaging equipment were poorly suited for use in children.  $^{131}\text{I}$  and  $^{197}\text{Hg}$ , for example, had high energies and long half-lives. Knowledgeable individuals at the time were also increasingly concerned about the sensitivity of developing tissues to the effects of radiation and the possibility of sequelae over the longer life span of the child. The result was a somewhat conservative approach that limited the use of radioisotopes in the pediatric population.

In 1955, George V. Taplin, MD, at the University of California at Los Angeles reported on the use of  $^{131}\text{I}$ -labeled rose bengal to study liver function (4). With C.C. Winter, MD, a urologist, Taplin in 1956 reported on the use of  $^{131}\text{I}$ -labeled diodrast to study renal function with scintillation probes (5,6). These procedures further laid the



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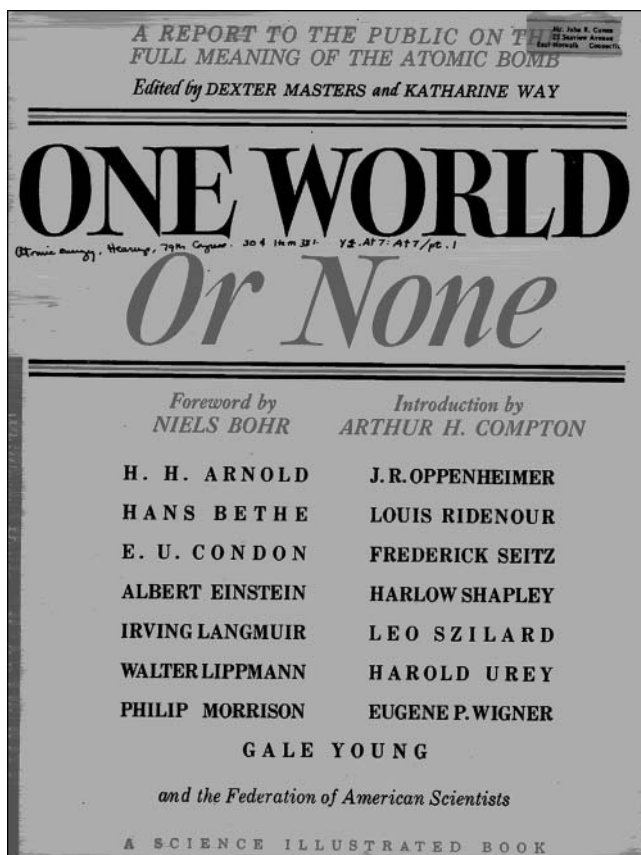


FIGURE 1. The *One Word or None* booklet.

foundation for the beginnings of routine pediatric nuclear medicine.

In 1954, medical student David Kuhl introduced the photorecorder that allowed the transfer of scintillation events in a crystal into a visual plot or image. This would prove to be an important element in the development of the rectilinear scanner. Benedict Cassen, MD, invented the rectilinear scanner, which "painted" a picture of radioisotope distribution in the patient's body (7).

One of the first pediatric practitioners to routinely use radioisotopes in children for imaging was Mel Tefft, MD, a radiotherapist at the Boston Children's Hospital (MA). In the early 1960s, he imaged the brain and other organs with a rectilinear scanner and  $^{197}\text{Hg}$  (8). For lack of space, his scanner was set up in a corridor outside the radiotherapy department.

Two signal events accelerated the development of the subspecialty of pediatric nuclear medicine. The first was the invention of the gamma camera by Hal Anger, who developed his prototype cameras at the Donner Laboratory in California between 1952 and 1958 (9,10). Alex Gottschalk, MD, joined Anger at the Donner Laboratory in 1962 and studied a few children with the prototypes. The gamma camera was especially suited for pediatric imaging because of its dynamic capabilities and an 8-inch field of view that was large enough to encompass most organs in the child. Images

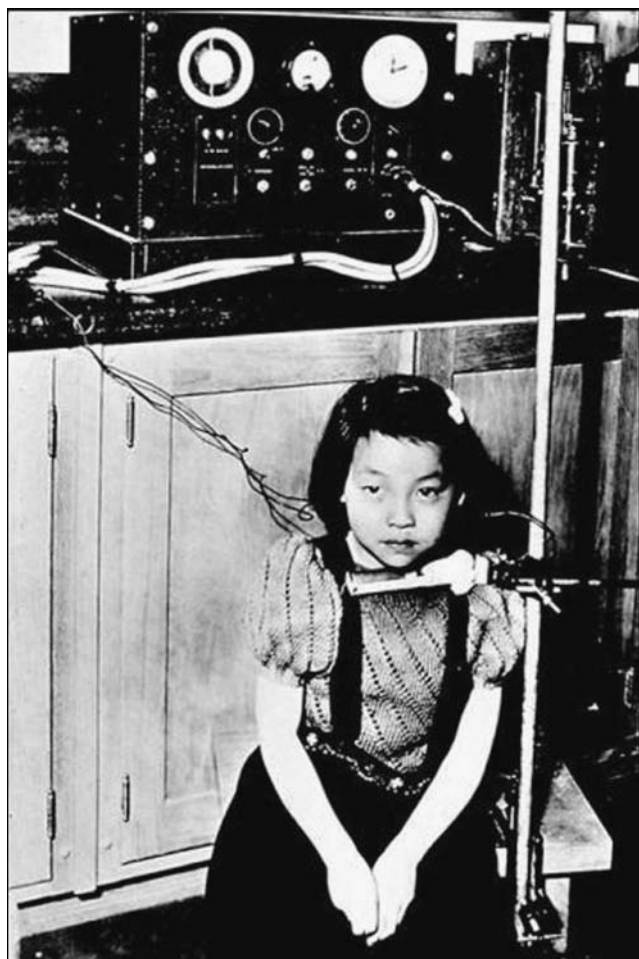


FIGURE 2. Thyroid uptake in a child.

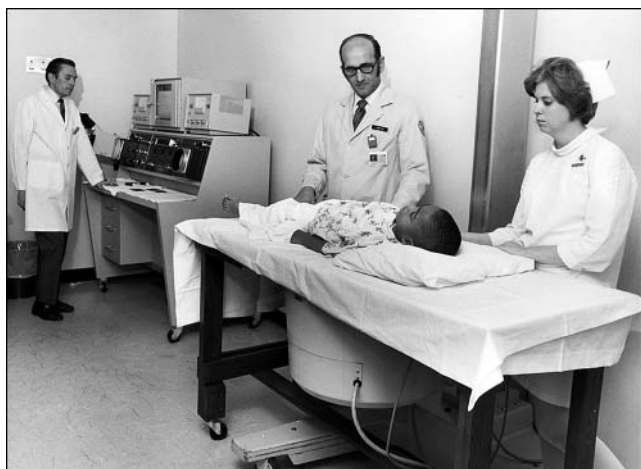
could be obtained in a matter of seconds to minutes rather than an hour or more with the rectilinear scanner.

John Kuranz, a founder of the Nuclear-Chicago Corporation in Chicago, IL, recognized the potential of the gamma camera for medical imaging. His company supported the development of the first commercially available 8-inch scintillation crystal, 19-photomultiplier tube gamma camera, installed in 1962 for William Myers, MD, at the Ohio State University Hospital at Columbus. The gamma camera allowed dynamic imaging of renal function, a major impetus to the use of radioisotopes in children. Pioneers such as Taplin, Winter, Keith Britton, MD, Gerald Burke, MD, Arlene Halko, MD, and John Harbert, MD, reported on the use of dynamic renal scintigraphy and renography with the gamma camera in the early to mid 1960s.

Burke and Halko at the Michael Reese Hospital in Chicago published the first report on the use of an 11-inch gamma camera to produce a  $^{131}\text{I}$ -iodohippurate renogram. They first localized the kidneys with an injection of  $^{203}\text{Hg}$ -chlormerodrin, and each kidney then was studied separately by positioning the kidney in the center of the field and administering separate injections of the radioiodinated hippuran (11).

In the late 1960s, Nuclear-Chicago modified the electronics of their 19-inch Pho Gamma III camera to “split the crystal,” so that both kidneys could be viewed simultaneously and the radioactivity counts from each kidney could be recorded separately on a graph chart recorder. The larger size of the Pho Gamma III camera was ideal for children. At Children’s Memorial in Chicago, we soon availed ourselves of the “split crystal technique” for renography (Figs. 3, 4). We improvised the technique of a 2-minute image with the Polaroid camera, which revealed any mispositioning so that we could easily adjust the child to recover the remainder of the renogram. Serendipitously, we recognized that the 2-minute image was a wonderful monitor for determining the glomerular function rate (GFR) of the kidneys. With experience, I could fairly accurately estimate the GFR by simply viewing the image. I believe that the results from this technique were about as accurate as all the later GFR techniques, many of which are still controversial. The later instrumentation advances of the tape recorder device and data recorder with region of interest instrumentation removed the need for special skills to position the child on the camera or to image kidneys not in their normal position.

The second major development in the early 1960s was the clinical introduction of  $^{99m}\text{Tc}$ -pertechnetate by Paul Harper, MD, a general surgeon, and his colleagues at the hospital of the University of Chicago (12). The 140-keV energy emission of  $^{99m}\text{Tc}$  allowed penetration of most body organs. The efficient energy absorption in the thinner crystal of the gamma camera increased the image resolution, and the short effective half-life of the radioisotope allowed its use in children.



**FIGURE 3.** A 1969 photograph of the Nuclear-Chicago Pho Gamma III camera with dual rate meters and a graph chart recorder. The wooden table was constructed by our hospital carpenters with a hole cut out to fit the collimator so the child could lie directly upon the collimator for the highest resolution possible. Renography was performed using the split crystal technique.



**FIGURE 4.** The Nuclear-Chicago Data recorder (broad arrow) with regions of interest capability eliminated the dual chart recorders and graph display. The tape recorder eliminated positioning errors in renography.

### Important Early Pediatric Nuclear Medicine Events

Webster’s *New World Dictionary* indicates that the word “pioneer” is from the old French for “a foot soldier or a peon.” Perhaps the most appropriate definition for a pioneer is “a person who goes before, preparing the way for others, as an early settler or a scientist doing exploratory work.” The following individuals’ innovations and publications are the ones that remain in my memory and that molded my clinical practice.

$^{99m}\text{Tc}$ -pertechnetate for scintillation imaging rapidly replaced  $^{197}\text{Hg}$  as the choice for studies of the brain. Among pioneers in imaging the pediatric brain were Kuhl and Richard Benua, MD (13,14). Fred Mishkin, MD, and John Mealey, Jr., MD, at the Riley Children’s Hospital in Indianapolis, IN, began rectilinear brain scanning in 1963, first with  $^{197}\text{Hg}$  and then with  $^{99m}\text{Tc}$ -pertechnetate. By 1967, they were performing more than 150 brain studies per year. Their book, *Use and Interpretation of the Brain Scan*, was published in 1969 and includes a chapter on pediatric conditions and findings (15).

Larry D. Samuels, MD, at the Children’s Hospital of Columbus, OH, was a prolific writer. He began his practice in the mid 1960s and published at least 37 papers on the use of radioisotopes in children between 1968 and 1972 (16). Many of his publications presented his experience with radioisotope investigations of liver and renal disease.

The number of studies and innovative techniques in pediatric nuclear medicine increased significantly between 1963 and 1972. In 1971, the first dedicated pediatric nuclear medicine symposium was held at Johns Hopkins in Baltimore, MD. The presentations at the symposium resulted in the first pediatric nuclear medicine text, with contributions from 85 authors representing both pediatric and adult practice. Published in 1974, the book was edited by A. Everette James, MD, Henry N. Wagner, Jr., MD, and Robert E. Cooke, MD (17).

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In 1971, Gopal “Mani” Subramanian, PhD, and John McAfee, MD, developed  $^{99m}\text{Tc}$ -polyphosphate for skeletal scintigraphy (18). Pediatric nuclear medicine took a giant step forward with the  $^{99m}\text{Tc}$ -labeled phosphate radiopharmaceuticals. The lower total-body absorbed dose from this class of radiopharmaceuticals enabled the study of benign disorders of the skeletal system in children. The characteristics of  $^{18}\text{F}$  for bone scintigraphy had restricted its use in children to the study of bone cancer and metastases. The  $^{99m}\text{Tc}$ -phosphate radiopharmaceuticals allowed additional studies of bone and soft tissue disorders, including infection, trauma, and sports injuries.

In October 1972 and January 1973, *Seminars in Nuclear Medicine* devoted issues to pediatric nuclear medicine. I was honored to serve as guest editor for those issues, which were combined in 1975 as a text published by Leonard Freeman, MD, and Donald Blafox, MD (19).

In 1973, Hirsch Handmaker, MD, and Jerold Lowenstein, MD, hosted a pediatric nuclear medicine symposium at the Children’s Hospital of San Francisco (CA). A multiauthor book representing the proceedings of that conference followed in 1975 (20).

Many other advances have forwarded the cause of pediatric nuclear medicine. Among these are the works of Massoud Majd, MD, who publicized the importance of phenobarbital in preparation for hepatobiliary scintigraphy in children with persistent neonatal jaundice (21). He is also recognized for his research in a swine model documenting that defects visualized with renal cortical scintigraphy are localized in sites of pyelonephritis (22). Majd also was an early pioneer in the use of captopril for the diagnosis of renovascular hypertension in children (23). George Sfakianakis, MD, popularized this technique (24).

Ted Harcke, MD, and Gerald Mandel, MD, published on a variety of subjects affecting the musculoskeletal system, drawing on their experience at the Alfred I. DuPont Institute for Children in Wilmington, DE. Harcke promoted intraoperative probe monitoring for surgical removal of osteoid osteoma and other tumors in difficult-to-reach but critical areas, such as the spine. He traveled at his own expense to many institutions, including our own, to assist practitioners in setting up the handheld scintillation probe detector to perform the procedure correctly (25).

In 1970, while attempting to image appendicitis with  $^{99m}\text{Tc}$ -pertechnetate, T.C. Jewett, MD, a surgeon, and Diane Duszynski, MD, at Buffalo Children’s Hospital (NY), recognized this as a valuable approach for localizing Meckel’s diverticulum (26,27). T.H. Berquist, MD, would report in 1973 that this radiotracer localized in ectopic gastric mucosa in the “Barrett’s” lesion of the esophagus (28). In our own studies of several children with “Barrett’s esophagus,” we found that  $^{99m}\text{Tc}$ -pertechnetate did not always localize in the lesion. Biopsy or surgical removal of the stricture lesions demonstrated a lack of mucosal cells in those lesions. These strictures were the result of metaplasia from gastroesophageal

reflux and not a true ectopic gastric mucosa, as Barrett originally described. Tapan Chadhuri, MD, did excellent research on animals and proved that it was the mucous cell in the gastric mucosa that localized the  $^{99m}\text{Tc}$ -pertechnetate. (29). The “mucous cells” in the colon do not localize the radioisotope, and I always used that as an example to teach the functional rather than the anatomic aspect of nuclear medicine. I published our experience with Meckel’s diverticulum in 1980, and Sfakianakis and I conducted a comprehensive 10-year revue of Meckel’s diverticulum scintigraphy to point out the immense value of that technique for imaging of rectal bleeding in children (30–32).

Larry Holder, MD, in Baltimore, MD, and others published important works on scrotal scintigraphy (33). The test took less than 30 minutes and had a high degree of accuracy in differentiating the various disorders. The surest means of determining torsion of the testicle had previously been by surgery, with many nonsurgical conditions mimicking torsion and proceeding to unnecessary intervention. Today, scrotal scintigraphy has been replaced by techniques with color Doppler ultrasonography.

S. Ted Treves, MD, developed the method for accurately and noninvasively quantifying left-to-right cardiac shunts in children (34,35). This innovation provided cardiologists with a means of measuring and monitoring the severity of shunts within the heart.

David Gilday, MD, and Judith Ash, MD, in Toronto, Ontario, have published extensively on all aspects of pediatric nuclear medicine and have represented the field throughout the world in their lectures and presentations.

In 1983, Jack Sty, MD, and Robert Starshak, MD, at Milwaukee Children’s Hospital (WI) recognized the value of bone scintigraphy in detecting child abuse, an approach we reviewed in an article in *Seminars in Nuclear Medicine* (36,37). From a legal aspect, the number of lesions that are detected has a significant impact on the outcome of court trials. Bone scintigraphy is a much more sensitive detector of abuse lesions than is plain radiography. In fact, we demonstrated that anterior rib lesions are just as common as posterior rib lesions but are poorly recognized by X-rays. I was summoned to court in a number of abuse cases and found that demonstrating 5 or 10 lesions rather than 1 or 2 provided compelling evidence of child abuse.

Sty and I published a review article on the use of radionuclides in the evaluation of the spleen in children (38). R.G. Wells, MD, and Sty also published an excellent review of the role of nuclear medicine in the screening of neonates with thyroid disorders (39). Sty’s books on pediatric nuclear medicine imaging have set the standard for quality and offer an extensive bibliographic reference source for almost every procedure in pediatric nuclear medicine. His books in my library are worn and broken from use (40,41).

James Kereiakis, PhD, Eugene Saenger, MD, and Henry Wellman, MD, pioneered radioisotope dosimetry calculation studies in children (42). Wellman also was a pioneer in promoting the use of  $^{123}\text{I}$  radiopharmaceuticals.

From 1963 through 1972, new pediatric techniques were introduced by many other “pioneers,” including Leonard Rosenthal, MD, Michael J. Gelfand, MD, Joe Leonard, MD, Meg Parisi, MD, Helen Nadel, MD, and John Miller, MD. At the time, many researchers who believed they had developed new techniques had only to search the literature to discover that Rosenthal had done the same thing years before.

The University of Michigan group, under the leadership of William Beierwaltes, MD, contributed significantly to the welfare of children with their development and promotion of iodinated metaiodobenzylguanidine for the study of neuroendocrine tumors (43).

Kuhl, with engineer Roy Edwards, developed the first computed axial tomograph at the Hospital of the University of Pennsylvania in 1964 (44). The first emission computed tomography image of a human was acquired in 1966. SPECT and PET evolved from Kuhl’s concepts.

A number of individuals who primarily focused on adult nuclear medicine have also made significant contributions to pediatric practice. Among these were: John Freitas, MD, and his colleagues who pioneered radioisotope thyroid therapy in children for hyperthyroidism; Beierwaltes, who reported on the long-term consequences of radioisotope therapy in children; Phil Alderson, MD, who performed pediatric lung and cardiac studies in children; and Naomi Alazraki, MD, and Andrew “Tip” Taylor, MD, noted for work in developing  $^{99m}\text{Tc}$ -mercaptoacetyltryglycine ( $^{99m}\text{Tc}$ -MAG3), an ideal radiopharmaceutical for renal imaging in children (45–47).  $^{99m}\text{Tc}$ -MAG3 was one of the first radiopharmaceuticals approved by the U.S. Food and Drug Administration for use in children. This approval was subsequent to prospective phase III clinical trials sponsored by Mallinckrodt, Inc. Sue Weiss, CNMT, James Halama, PhD, James Everett, CNMT, and I furnished the phase III absorbed radiation dosage measurements for  $^{99m}\text{Tc}$ -MAG3 for the various age levels from infancy to teens (48).

Other significant contributors to the advancement of pediatric nuclear medicine include Gary Gates, MD, John Miller, MD, Richard Spencer, MD, Martin Charron, MD, Barry Shulkin, MD, Harriet Paltiel, MD, Rick Shore, MD, Monica Rossleigh, MD, Sidney Heyman, MD, and others.

Among the international contributors who come to mind are Gian Carlo Mussa, MD, of Torino, Italy, who primarily studied neonates; Rune Sixt, MD, in Sweden; Amnon (Amy) Piepsz, MD, in Brussels, Belgium; Isky Gordon, MD, and Andrew Hilson, MD, in England; Klaus Hahn, MD, in Munich, Germany, who has sponsored several pediatric nuclear medicine conferences and published an atlas of pediatric nuclear medicine; Joe Savage, MD, Robert Howman-Giles, MD, Shane Moroney, MD, and Proven Murray, MD, in Australia; Homai Da Costa, in Bombay, India; Daniel Schere, MD, in Buenos Aires, Argentina; Isabel Roca, MD, in Spain, who has conducted pediatric nuclear medicine meetings in recent years, and Enrique Olea, MD, in Santiago, Chile. Unfortunately, space

does not permit appropriate recognition of many other practitioners and events.

The early innovations could not have been achieved without pioneer pediatric nuclear medicine technologists. Among the most notable were Weiss, in Chicago; Elizabeth Kilburn, RTNM, in Toronto; Royal Davis, CNMT, in Boston, MA; George Hoebring in Kansas City, MO; Barbro Ljung in Sweden; and Jill Freeman, Michele Maher, and Heather Bauer in Australia.

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