# Potential Column Chromatography Generators for Ionic Ga-68.

## I. Inorganic Substrates

Rudi D. Neirinckx and Michael A. Davis

*Harvard Medical School and Children's Hospital Medical Center, Boston, Massachusetts*

**Chemical separations for Ga-68 from Ge-68 using adsorption chromatography on inorganic materials are described. The adsorbents used were $TiO_2$, $ZrO_2$, and $SiO_2$. Distribution coefficients for Ge and Ga on these adsorbents were determined as a function of reagent concentration and duration of equilibration. The distribution coefficient (w/w) for Ge on $SiO_2$ reached 250 in 6 *N* $HNO_3$, whereas Ga was not significantly adsorbed. Therefore, Ga-68 can be collected with a small volume of 6 *N* $HNO_3$ eluent. By contrast, large volumes of 1 *N* $HNO_3$ were necessary to collect Ga-68 from $ZrO_2$, since the $K_D$ of Ga under these circumstances was about 50. The Ga-68 eluted from $TiO_2$ was chemically contaminated with titanates and would require additional chemical manipulation in order to make it injectable. All the adsorbents could lead to chromatographic systems that would allow acceptable chemical separations. However, the specific requirements for a radionuclide generator, usable in a hospital environment, make the $SiO_2$-based system the most attractive.**

**J Nucl Med 20: 1075–1079, 1979**

With the development of emission tomographic reconstruction methods, interest in the diagnostic use of positron-emitting radionuclides has increased. Annihilation coincidence detection allows "electronic" collimation and thus each detector is able to record radiation emitted in many different directions. This affords a tremendous increase in geometric detection efficiency over single-photon counting procedures (*1,2*). The very short-lived positron emitters C-11, N-13, and O-15 are cyclotron-produced and therefore unavailable in most hospital settings. Gallium-68, a radionuclide with a 68-min half-life, is accessible by means of a generator system based on its separation from the parent Ge-68 (half-life 287 days). The 68-min half-life is sufficiently short to provide reasonably low radiation exposure to the patient, yet long enough to permit the synthesis of radiopharmaceuticals that could be used to study a variety of physiologic functions.

In principle, a radionuclide generator system designed for use in nuclear medicine should be simple, and reproducibly give a high yield of the desired radionuclide with a very large separation factor from the parent. The eluate should be injectable or easily converted to an injectable form. The collection of the daughter nuclide should be possible with a small volume of reagent.

The method most frequently used for the analytical separation of microgram and milligram quantities of Ge from other elements is based on extraction or distillation. Extractions of Ge in carbon tetrachloride (*3*), methyl isobutyl ketone (*4,5*), and acetyl acetone (*6*), and by means of an oxine complex (*7*), are well established, as is the distillation of germanium tetrachloride (*8,9*) or germanium hydride (*10*). The distillation of germanium tetrachloride has recently been used as the separation mode in a Ge-68 → Ga-68 generator (*11*), but the 0.5% loss of Ge and the more complicated nature of the distillation procedure make this more useful in a research

---

Received Jan. 23, 1979; revision accepted May 7, 1979.

For reprints contact: Rudi D. Neirinckx, Dept. of Radiology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115.

environment than in a typical hospital setting.

The most practical techniques for chemical separation under carrier-free conditions are those of column chromatography—mainly ion-exchange or adsorption chromatography systems. Ion-exchange chromatographic procedures are hampered by the nonionic character of most germanium compounds. Even $GeCl_4$ has covalent bonds and can be extracted with organic solvents. On cation exchange resins such as Dowex 50, Ge is not even retained from dilute hydrochloric acid solution. Though this property has been used to separate Ge from other elements, the procedure does not lend itself to the development of a Ge-68 → Ga-68 generator, since this calls for strong Ge adsorption. On strongly basic anion exchangers, like Bio-Rad AG1, Ge is retained from a hydrochloric acid concentration range in which Ga is also strongly adsorbed.

The fixation of Ge onto substrates has not been encouraging and has been avoided in analytical chemistry. In the currently available Ge-68 → Ga-68 generator, developed by Greene and Tucker, Ge-68 is loaded onto an aluminum oxide support and the Ga-68 is eluted as a strong Ga-68-EDTA complex using a 5-m*M* EDTA solution at pH 7.0 (*12*). Other workers have attempted to produce alternative column chromatographic methods for obtaining a simple ionic form of Ga-68 in solution. Kopecky et al. (*13*) eluted an $Al_2O_3$ (basic; Merck) column with 0.2 *M* HCl, collecting 48% of the Ga-68. Up to 200 elutions were performed, and the aluminum and Ge-68 contaminants of the eluate assayed. The Ge-68 level was less than $2 \times 10^{-3}\%$ of the Ga-68. In a Ga-68-labeled colloid for liver scanning this would increase the radiation dose by about 25%. Malyshev et al. (*14*) used the hydroxides of zirconium, tin, and titanium as adsorbents, and either HCl, $HNO_3$, or $CH_3COOH$ as eluents. The optimum was found to be a zirconium hydroxide adsorbent eluted with 0.1 *M* HCl. A 35% yield of Ga-68 was obtained with the Ge-68 breakthrough varying from $6 \times 10^{-3}$ to $3 \times 10^{-2}\%$. With Ga-68-labeled colloids this breakthrough would lead to increases of dose rate to the liver of 75 to 400%, respectively. Arino et al. (*15*) adsorbed Ge-68 on polyantimonic acid and eluted Ga-68 with 2% sodium oxalate. The loss of Ge-68 from the substrate, the toxicity of the eluent, and the complex character of the Ga-68 product would make this system unacceptable for clinical use without further chemical manipulation.

## MATERIALS AND METHODS

Germanium dioxide adopts either the tetrahedral or octahedral valence state, crystallizing in a quartz or rutile lattice, respectively. The rutile lattice is stable below 1033°C and is soluble in water. We investigated the possible adsorption of germanium dioxide on either silicon dioxide (quartz lattice) or titanium dioxide (rutile lattice).

Hydrous zirconium oxide was also tested as a column support. It is the basis for the currently used Sn-113 → In-113m generator. Since their positions in the periodic table indicate that there are some similarities between the Ge-68 → Ga-68 and the Sn-113 → In-113m pairs, this substrate was examined as a potential chromatographic column.

Two hundred milligrams of either titanium dioxide ($TiO_2$), hydrous zirconium oxide ($ZrO_2$), or silica gel ($SiO_2$) were shaken with 5-g aqueous solutions of Ge-68, and the $K_D$ values determined as a function of the pH or the concentration of $HNO_3$. Ge-68 → Ga-68 was added to the liquid phase before equilibration. After equilibration the gallium distribution was corrected for decay in the liquid phase and ingrowth of activity on the substrate, taking into account the distribution of Ge-68 over both fractions. The germanium distribution was measured by counting the Ga-68 activity in both fractions 24 hr after the end of the equilibration. Distribution coefficients ($K_D$) were calculated as:

$$K_D = \frac{\text{activity/gram of adsorbent}}{\text{activity/gram of eluent}}$$

**Titanium dioxide.** Titania powder*, ground titanium dioxide crystals, and calcium titanate were used as adsorbents for Ge. The distribution coefficients for Ge and Ga were studied as a function of the pH of the eluent, which was adjusted by means of sodium hydroxide or sodium phosphate buffers.

**Hydrous zirconium oxide.** The adsorption of Ge and Ga on hydrous zirconium oxide from dilute $HNO_3$ was measured as a function of both the nitric acid concentration and time. The latter was necessary since it was observed during the course of the work that the adsorption of both elements on $ZrO_2$ is a slow process.

**Silicon dioxide.** Distribution coefficients for both Ge and Ga on $SiO_2$† were measured as a function of the normality of $HNO_3$. Since it was found that the adsorption of Ge is a slow process, the distribution coefficients of both elements were studied as a function of the equilibration time.

## RESULTS

**Titanium dioxide.** Figure 1 shows the distribution coefficients for titanium dioxide as a function of pH. In the pH range from 5 to 7, Ga is more strongly adsorbed than Ge. The $K_D$ for Ge rises rapidly with increasing pH, reaches 2,500 around pH 7.5, and stays above 2,500 up to pH 12. The $K_D$ for Ga stays higher than 2,500 up to about pH 9.5, then decreases rapidly with increasing pH. For pH values above 10.5, the $K_D$ for Ga is lower than 10, whereas that for Ge is higher than 2,500.

**Hydrous zirconium oxide.** Figure 2 shows the distribution coefficients for Ge and Ga adsorbed on $ZrO_2$ from 0.5 *N* and 1 *N* $HNO_3$, measured as a function of time. After a 2-hr equilibration period, the adsorption

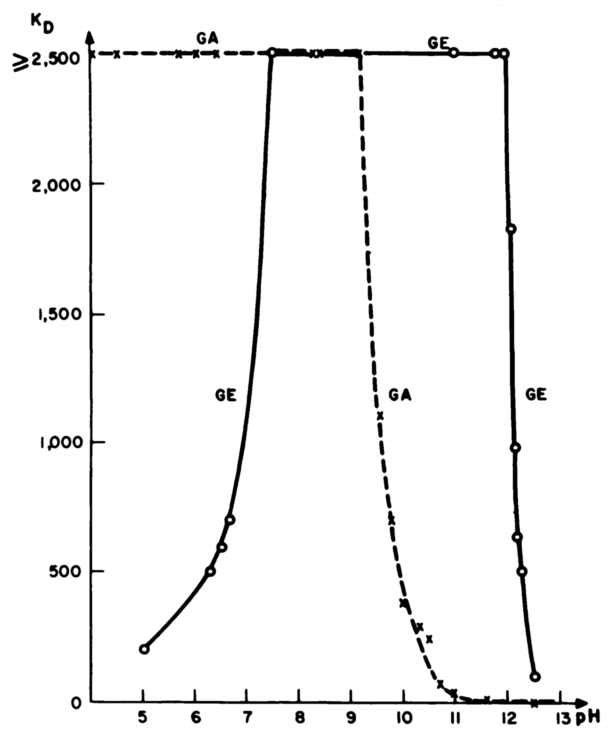

**FIG. 1.** $K_D$ between $TiO_2$ and aqueous solutions for Ge and Ga as function of pH. (Reprinted from ref. 17 with permission from John Wiley & Sons.)

of neither Ge nor Ga has reached its maximum, as determined by desorption experiments with Ge, adsorbed previously onto $ZrO_2$. The collection of Ga from a generator will be influenced by the degree of its desorption from $ZrO_2$. Figure 3 indicates the distribution coefficients for Ge and Ga, determined by desorption from $ZrO_2$, as a function of $HNO_3$ concentration. It suggests that a good separation of Ga from Ge is theoretically possible, but it would require large volumes of dilute $HNO_3$.

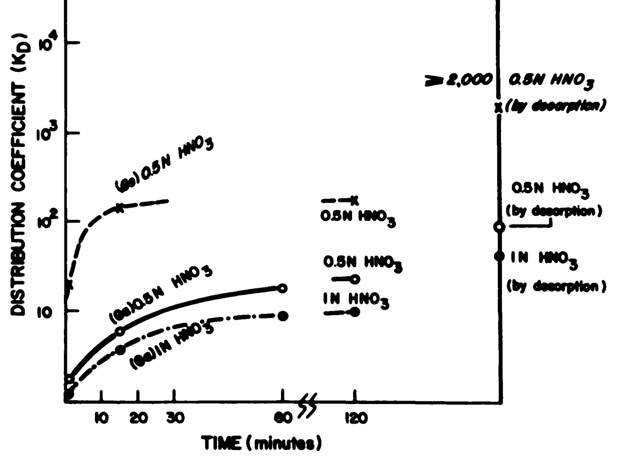

**FIG. 2.** $K_D$ between $ZrO_2$ and dilute $HNO_3$ for Ge and Ga as function of equilibration time.

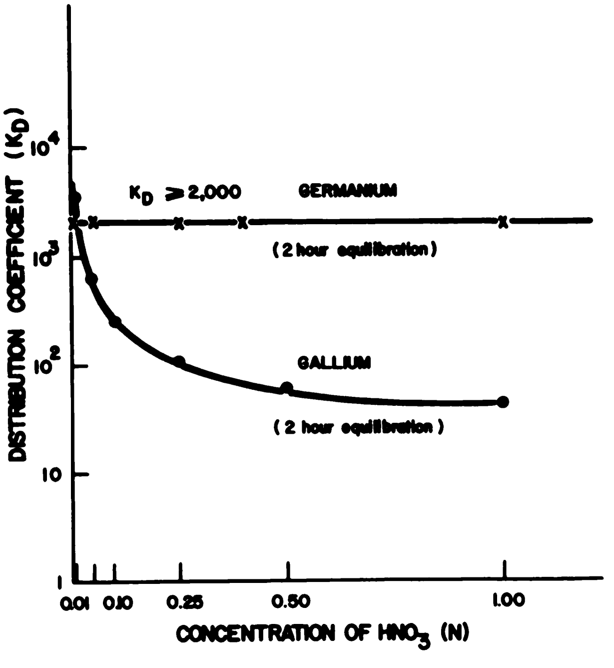

**FIG 3.** $K_D$ between $ZrO_2$ and $HNO_3$ for Ge and Ga, measured by desorption, as function of $HNO_3$ concentration.

**Silicon dioxide.** Figure 4 shows the steady rise in the distribution coefficient of Ge between $SiO_2$ and $HNO_3$ with increasing equilibration times. After about 15 min of equilibration, Ge reaches its maximum adsorption, which is measured by its desorption from $SiO_2$, on which it has been previously loaded. Gallium does not show such an effect. The adsorption is very low over the whole time span measured, and desorption experiments also show that it is weakly adsorbed onto $SiO_2$. Figure 5 shows the distribution coefficients for Ga and Ge on $SiO_2$ as a function of the normality of the $HNO_3$ solution, measured by desorption batch equilibration. The adsorption of Ge increases quickly with increasing $HNO_3$ concentration, whereas that of Ga remains negligible.

## DISCUSSION

Although the three systems described provide a good chemical separation of Ga from Ge, only the $SiO_2$-based separation would be acceptable for a generator system. In the pH interval from 10.5 to 12, $TiO_2$ allows a separation in a reasonable volume, but $TiO_2$ dissolves slowly in dilute alkaline media, and more quickly at higher pH. Fine particles of titania are formed, tending to clog the chromatographic column. This leads to the appearance of unwanted titanates in the Ga-68 solution. Calcium titanate, which generally dissolves less easily than titanium dioxide, also proves too soluble in alkaline media to provide any improvement over titania powder. Al-

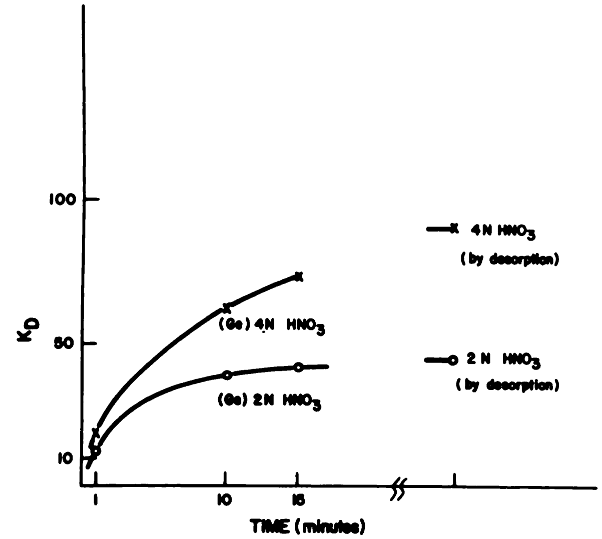

FIG. 4. $K_D$ between $SiO_2$ and $HNO_3$ for Ge as function of equilibration time.

though these titanates might not interfere with the preparation of Ga-68-labeled radiopharmaceuticals, their presence would necessitate additional chemical manipulation to ascertain the injectability of the pharmaceutical preparation. The $K_D$ values for Ga on $TiO_2$ indicate that the $TiO_2$ substrate adsorbs Ga very strongly between pH 4 and 9.5. Gallium occurs as $Ga(OH)_3$ in the pH interval between 3.4 and 9.7 (*16*), indicating that the Ga-68 species adsorbed onto the $TiO_2$ is the trihydroxide. At higher pH values the gallium species eluted from the $TiO_2$ may be $HGaO_3^{2-}$ or $H_2GaO_3^-$ (*16*). At still higher pH values, gallates with composition of either $Ga_2(OH)_8^{2-}$ (*16*) or $GaO_2^-$ may be present.

The $ZrO_2$-based separation requires large volumes of eluent in order to collect Ga-68 from a generator. The distribution constants for Ga drop with increasing normality of the nitric acid solution (Fig. 3). However, separations at concentrations higher than 1 *N* $HNO_3$ are impractical, since $ZrO_2$ dissolves at these higher concentrations. When $H_2O_2$ is added to the eluent it is decomposed by the $ZrO_2$. Elution with nitrate solutions having pH values between 6.5 and 10.5 does not collect the gallium, while with mixtures of dilute HF ($10^{-3}$ *N*) and dilute HCl ($10^{-4}$ *N*) the $K_D$ values for germanium are too low to be practical for a generator.

The incorporation of Ge-68 into $SiO_2$ is carried out by precipitation of $SiO_2$ from a solution containing Ge-68. The elution yields of gallium-68 with $H_2O$, HCl, and $HNO_3$ are low. The $SiO_2$ column washed with $HNO_3$ is the most satisfactory chromatographic system. Generally, the $K_D$ values increase as a function of the period of equilibration and are higher in more concentrated $HNO_3$. The increases could be due to a slow reaction of Ge with $HNO_3$ to form germanium compounds that adsorb strongly on $SiO_2$. These could be metagermanates

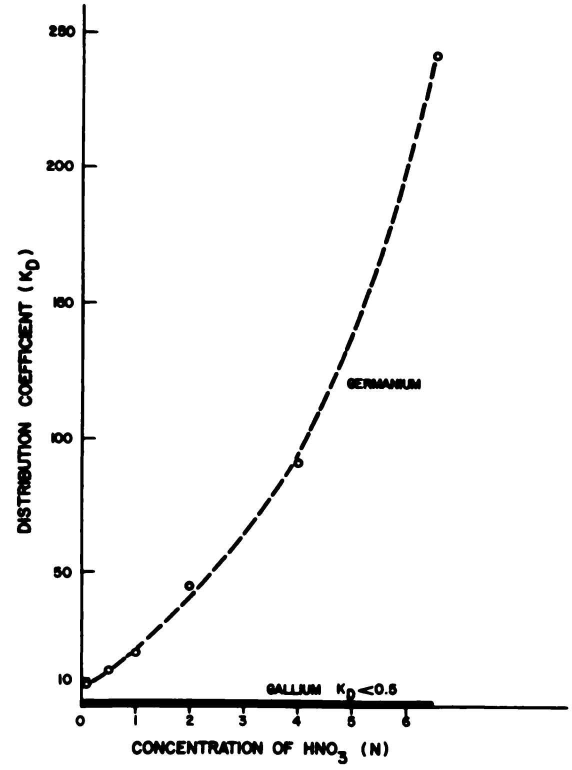

FIG. 5. $K_D$ between $SiO_2$ and $HNO_3$ for Ge and Ga as function of $HNO_3$ concentration.

($M_2^IGeO_3$) or orthogermanates ($M_2^{II}GeO_4$), which have structures analogous to the corresponding meta- and orthosilicates. In dilute solutions the principal germanium compounds probably are $[GeO(OH)_3]^-$, $[GeO_2(OH)_2]^{2-}$, and $\{[Ge(OH)_4]_8(OH)_3\}^{3-}$, which might be only weakly or not at all adsorbed on $SiO_2$. The conversion to the meta- and orthogermanates could be slow; heating speeds up the process. A 0.49 *N* $HNO_3$ solution of Ge, heated to boiling for 1 min, leads to a germanium $K_D$ of 27 on $SiO_2$, while at room temperature it takes 2 hr to reach a $K_D$ of 13. A drawback of this generator system is the use of $HNO_3$. Nitrates may form carcinogenic nitrosamines, which would make the evaporation to dryness of the collected gallium fraction compulsory. In these circumstances Ga is not volatile unless the heating is extensively prolonged. After redissolution in the desired solute, the ionic Ga-68 could be used for labeling without further chemical manipulation. This is an advantage over the currently available generator, which delivers Ga-68 as a very stable Ga-EDTA complex. Even very small amounts of EDTA will strongly influence the behavior of Ga-68 preparations, so that the separation or destruction of the EDTA must be complete.

## FOOTNOTES

* Baker's Analyzed Titania.

† Merck Kieselgel 60F, 70-230 mesh, Merck, Sharp & Dohme, West Point, PA.

### ACKNOWLEDGMENT

This work was supported by the DOE Contract No. EY-76-S-4115. This material was presented in part at the Second International Symposium on Radiopharmaceutical Chemistry, July 1978, Oxford, England (*17*), at the Second International Symposium on Radiopharmaceuticals, March 1979, Seattle, Washington, and at the joint American Chemical Society-Chemical Society of Japan Chemical Congress, April 1979, Honolulu, Hawaii.

### REFERENCES

1. PHELPS ME, HOFFMAN EJ, MULLANI NA, et al: Application of annihilation coincidence detection to transaxial reconstruction tomography. *J Nucl Med* 16: 210-224, 1975
2. BUDINGER TF, DERENZO SE, GULBERG GT: Emission computed axial tomography with single-photon and positron annihilation photon emitters. *J Comput Assist Tomogr* 1: 131-145, 1977
3. BRINK GO, KAFALAS P, SHARP RA, et al: Solvent extraction systems: I. Arsenic(III) and germanium(IV) in hydrochloric acid and arsenic(III) in hydroiodic acid with several solvents. *J Am Chem Soc* 79: 1303-1305, 1957
4. SENISE P, SANT' AGOSTINO L: Determination of germanium after extraction by methyl isobutyl ketone. I. *Mikrochim Acta:* 1445-1455, 1956
5. SENISE P, SANT' AGOSTINO L: Determination of germanium after extraction by methyl isobutyl ketone. II. *Mikrochim Acta:* 572-581, 1959
6. GLEASON GI: A positron cow. *Int J Appl Radiat Isot* 8: 90-94, 1960
7. ERHARDT GJ, WELCH MJ: A new germanium-68/gallium-68 generator. *J Nucl Med* 19: 925-929, 1978
8. BARTELMUS G, HECHT F: Microdetermination of germanium. *Mikrochim Acta:* 148-162, 1954
9. RAYNER HB: The quantitative recovery of germanium by distillation from hydrochloric acid in the presence of sodium chloride. *Anal Chem* 35: 1097-1098, 1963
10. COASE SA: Detection of small quantities of germanium in the presence of arsenic. *Analyst* 59: 747-749, 1934
11. MIRZADEH S, KAHN M, GRANT PM, et al: A distillation-based Ge-68/Ga-68 positron generator. In *Abstracts of the Second International Congress of the World Federation of Nuclear Medicine and Biology*. Washington DC, 1978, p 82
12. GREENE M, TUCKER W: An improved gallium-68 cow. *Int J Appl Radiat Isot* 12: 62-63, 1961
13. KOPECKY P, MUDROVA B: $^{68}$Ge-$^{68}$Ga generator for the production of $^{68}$Ga in an ionic form. *Int J Appl Radiat Isot* 25: 263-268, 1974
14. MALYSHEV KV, SMIRNOVV: A generator of gallium-68 based on zirconium hydroxide. *Radiokhimiya* (Engl. trans.) 17: 137-140, 1975
15. ARINO H, SKRABA WJ, KRAMER HH: A new $^{68}$Ge/$^{68}$Ga radioisotope generator system. *Int J Appl Radiat Isot* 29: 117-120, 1978
16. DYMOV AM, SAVOSTIN AP: Analytical chemistry of gallium. In *Analytical Chemistry of the Elements,* Vinogradov AP, ed. Ann Arbor, MI, Ann Arbor Science Publishers, 1970, pp 8-22
17. NEIRINCKX RD, DAVIS MA: Generator for ionic gallium-68. *J Label Comp Radiopharm:* (In press)

---

## NEW ENGLAND CHAPTER THE SOCIETY OF NUCLEAR MEDICINE FALL MEETING

**Oct. 13-14, 1979 Downtown Howard Johnsons Boston, Massachusetts**

The New England Chapter of the Society of Nuclear Medicine announces its Fall Meeting to be held Oct. 13-14, 1979, at the Downtown Howard Johnsons in Boston, Massachusetts.

Topics for lectures to be presented on Saturday include: a) Differential diagnosis of bone lesions, b) Early detection of gastrointestinal bleeding, c) Liver disease and biliary imaging, and d) Pediatric osteomyelitis and genito-urinary reflux. Workshop sessions will be concerned with Bone, Heart, Pediatrics, and Techniques.

On Sunday, following the presentation of the Blumgart Award to Dr. David Kuhl, there will be a symposium on "Tomographic Imaging."

For further information contact:

Dr. H. William Strauss
Dept. of Radiology
Div. of Nuclear Medicine
Massachusetts General Hospital
Boston, MA 02114