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NUCLEAR MEDICINE PROGRAM PROGRESS REPORT FOR QUARTER ENDING DECEMBER 31, 1988

F. F. (Russ) Knapp, Jr., Group Leader

K. R. Ambrose
A. P. Callahan
D. W. McPherson
P. C. Srivastava

J. F. Allred
S. L. Blystone
J. Kropp
E. C. Lisic
D. E. Rice
C. J. Rogers
G. Umbricht

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SUMMARY

A new project involving the development of production and processing technology for radionuclides of biomedical interest has been initiated in the Nuclear Medicine Program. This research supports the development of radioisotope production and processing technology and radionuclide generator systems to provide the technology required to make available radionuclides of biomedical interest. The principal focus is the evaluation of radioisotope reactor production modes, radiochemistry, and radioanalytical methods to provide radionuclides of high specific activity and radiochemical and chemical purity. This project complements the Nuclear Medicine and core Biomedical Radioisotope Technology Program which involves the design, development, and biological testing of new tissue-specific radiopharmaceuticals. The goal is to expand the capability at ORNL to produce medical radionuclides that are not commercially available using state-of-the-art technology. This project is not a production effort but a research and development activity to assess and solve problems associated with the production, processing, and availability of radionuclides of medical interest.

The synthesis of 15-(p-iodophenyl)-3-R,S-methyl-3-hydroxypentadecanoic acid (3-hydroxy BMIPP) is also described in this report. Comparison of the chromatographic properties of the polar metabolite isolated from isolated rat hearts administered iodine-125 BMIPP have demonstrated it to be more polar than 3-hydroxy BMIPP.

BIOMEDICAL RADIOISOTOPE TECHNOLOGY DEVELOPMENT

A new project in our Nuclear Medicine Program supports the development of radioisotope production and processing methods and radionuclide generator systems to provide the technology required to make available radionuclides of biomedical interest. Traditionally, our ORNL Nuclear Medicine Program has been involved in the design, development, and biological testing of new radiopharmaceuticals, which requires interaction with extramural Medical Cooperative Programs for further preclinical evaluation. The biomedical radioisotope development project involving cell processing, radiochemistry, gamma spectroscopy, and radionuclide generator development will expand and complement these aspects of our basic research program. This project is specifically directed at providing the expertise required for the development of radioisotope production technology in developing and optimizing production and processing procedures and in providing the cost estimates and technical assistance required to transfer these projects from a research effort to a routine production capability in the ORNL Isotopes Distribution Office (IDO).

Work in this area will focus primarily on reactor-produced radionuclides and will include evaluation of processing and production technology of radioisotopes of biomedical interest. These efforts will involve both direct production and the development of radionuclide generator systems from which daughter radionuclides of therapeutic or diagnostic interest are obtained. Our approach for this project includes development of production technology, encompassing target design, selection of production mode, and development and optimization of chemical processing. The necessary analytical procedures for evaluation of chemical and radiochemical purity will also be developed into detailed written procedures that can be adapted for routine production, and quality control procedures will be prepared. These procedures will be made available to radioisotope production groups at ORNL for production and distribution of radioisotopes through the IDO. Technical assistance will be provided as required to the ORNL Radioisotope Production personnel of the Chemical Technology Division to enhance transfer of this technology. Examples of efforts in this project are assistance in modifications of the processing and purification procedures to accommodate larger reactor targets and guidance in analytical and quality control procedures. Cost estimates for routine production will also be developed.

The High Flux Isotope Reactor (HFIR) represents an important resource for the production of a large number of radionuclides of biomedical interest. This facility was temporarily shut down in November 1986, which has necessitated alternative arrangements to obtain reactor-produced radioisotopes for our program. Personnel (David Rorer, Ph.D., and colleagues) at the Brookhaven

High Flux Beam Reactor (HFBR) have been extremely helpful in supplying radioisotopes required for a continuation of many of our research projects including the Os-191 and W-188 parent isotopes for the Os-191/Ir-191m and W-188/Re-188 radionuclide generator systems. In addition, the University of Missouri Research Reactor is providing irradiation services. Radioisotopes from these sources will continue to be used for our new technology development effort. Resumption of operation of the HFIR is an important milestone at ORNL for production of radioisotopes for this project. In addition, the Advanced Neutron Source (ANS) will represent a powerful and unique radioisotope production capability that will provide a very high thermal neutron flux (expected to be nearly 4-5 times that of the HFIR) when it becomes operational in the late 1990's. In addition to the production of radioisotopes with much higher specific activities, availability of the ANS will provide an important opportunity for conserving significant amounts of the enriched stable istopes required for radioisotope production.

Development and optimization of the production and processing procedures for radionuclides that are of interest for both therapeutic and diagnostic applications are being pursued. The radionuclides of therapeutic interest have a variety of applications. Currently, one of the most rapidly growing and important areas is the radiolabeling of tissue-specific antibodies for therapeutic applications. Because very small amounts of antibodies are often required, the availability of high specific activity radionuclides of high chemical purity is often a major factor determining suitability for practical use. For this reason, there is widespread interest in the availability of radionuclides for therapy via both direct production and radionuclide generator systems. Table 1 lists a variety of radionuclides of current interest that we are studying.

Table 1. Important Reactor-Produced Radionuclides for Therapeutic Applications

		Direct Production		
Radionuclide		T 1/2		Production Route
Re-186		90.4 h		Re-185(n,γ)Re-186
Cu-67		61.9 h		Zn-67(n,p)Cu-67
Sm-145		340 d		Sm-144(n,γ)Sm-145
Sm-153		46.7 h		Sm-152(n,γ)Sm-153
		From Radionuclide Generator Systems		
Daughter	T 1/2	Parent	T 1/2	Production Route
Re-188	16.9 h	W-188	69 d	W-186(n,γ)W-187(n,γ)W-188
Ir-194m	19.2 h	Os-194	6 y	Os-192(n,γ)Os-193(n,γ)Os-194

During the initial stages of this new effort, we have focussed on the optimization of the synthesis of platinum-191m-labeled cis-dichlorodiammine-platinum(II) (cis-DDP). Platinum-195m-labeled cis-DDP is in widespread demand for both pharmacological and clinical studies. The small-scale synthesis of this material was developed in our program several years ago (Hoeschele, et al., 1981). We have continued to provide the technical expertise to make Pt-195m cis-DDP available on a special order basis through the ORNL Isotopes Distribution Office on a cost recovery basis. Over the last 3-4 years, the demand has far exceeded our capability as part of the Nuclear Medicine and Biomedical Radioisotope Technology Program to supply this agent. Shutdown of the HFIR necessitated production of the Pt-195m in the University of Missouri Reactor on a service irradiation basis. Because of the lower neutron flux, specific activity of the Pt-195m is significantly decreased (1 mCi/mg → 0.2 mCi/mg), which has required alterations in the synthetic procedure because of the larger mass. The radiochemical and quality control procedures have been revised and optimized to accommodate the larger scale synthesis. New cost estimates have also been completed. We have now made available the procedures for routine production and distribution. To optimize our use of the reactor production capabilities available in the U.S., we are working closely with our colleagues at sister laboratories to project the optimal production sites for the radioisotopes of interest. Future aspects of this project will focus on the optimization and final development of the tungsten-188/rhenium-188 radionuclide generator for routine distribution. Copper-67 is routinely produced by spallation, but can contain significant levels of nonradioactive copper which cannot be removed, hence significantly decreasing the specific activity to about 6 mCi/μg/ppm copper in the target foil (Mirzadeh et al., 1986). Although production yields are much lower, reactor production of Cu-67 by the Zn-67(n,p)Cu-67 reaction overcomes problems associated with specific activity since carrier-free Cu-67 can be obtained. Routine reactor production would also ensure that Cu-67 would be available year-round, since production in the high-energy accelerators at BNL and LASL are often interrupted because of routine prolonged shutdowns. As an important example, radiolabeling of antibodies often requires very high specific activity radionuclides. Production of Cu-67 in the HFIR will be reassesed, procedures for purification of high levels of Cu-67 will be written, and quality control guidelines developed for routine production to fulfill future needs of this important radionuclide. The initial stages of this work have involved supplying enriched Zn-67 targets for irradiation at the HFBR at BNL with subsequent processing at ORNL.

RADIOIODINATED FATTY ACIDS – SYNTHESIS OF 15-(p-IODOPHENYL)-3-R,S-HYDROXY-3-METHYLPENTADECANOIC ACID (β-OH-BMIPP)

As described in an earlier report (ORNL/TM-10618), a synthesis of β-hydroxy fatty acids has been developed via the alkylation of "Meldrum's Acid" to provide these interesting standards to investigate the expected accumulation of fatty acid intermediates in ischemic myocardium. The accumulation of β-hydroxy-IPPA in oxygen-deprived heart tissue has not yet been investigated and could provide an important opportunity to further investigate the metabolic fate of this agent.

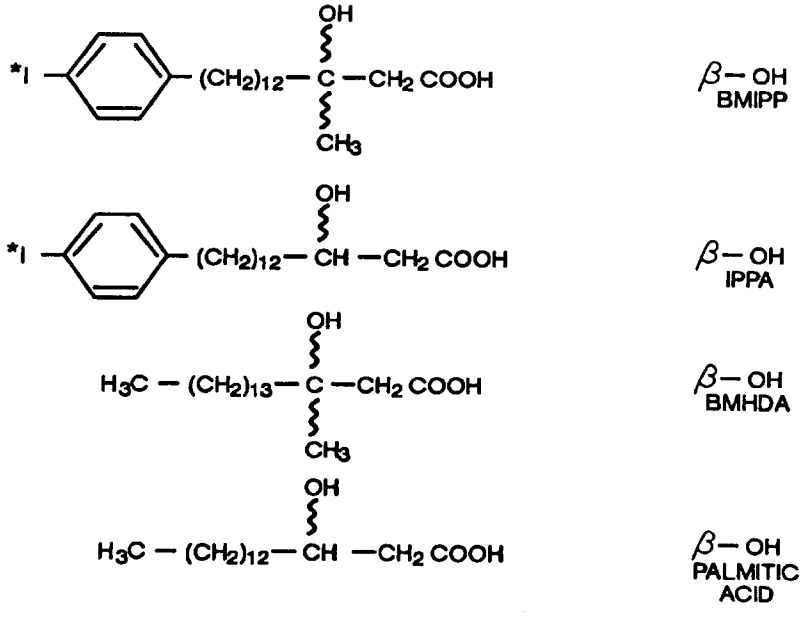
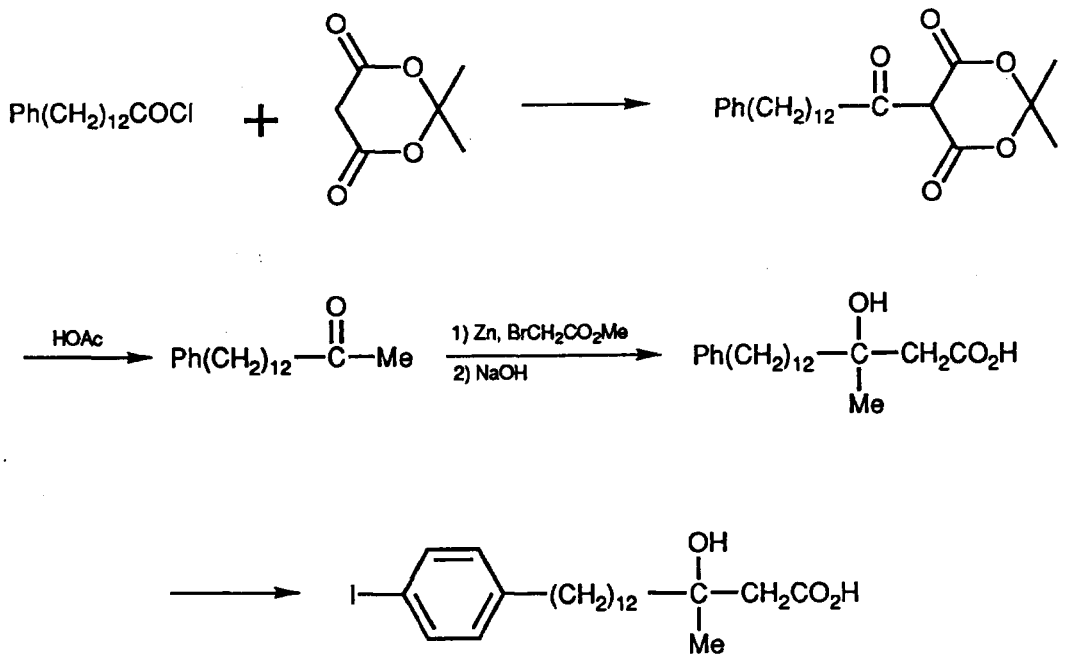


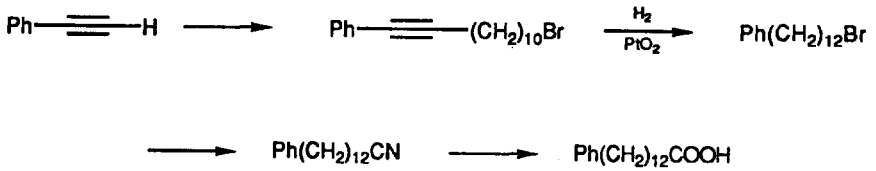
Figure 1. Structures of β-hydroxy fatty acids.

For fabrication of the 15-carbon chain length skeleton of IPPA and BMIPP, 13-phenyltridecanoic acid is the reguisite intermediate for attachment to the "Meldrum's Acid" template (Scheme I). Traditionally, we have prepared the 13-phenyltridecanoic acid via acylations



Scheme I

of a thiophene template followed by deoxygenation and subsequent reductive ring opening (ORNL/TM-10618). As an easier alternative route, we have now utilized a published procedure[1] initiated via the alkylation of phenylacetylene as shown in Scheme II. Synthesis of larger amounts of 15-phenyl-3-R,S-hydroxy-3-methylpentadecanoic acid (ß-OH-BMIPP) have provided sufficient substrate for introduction of iodine into the para-position to prepare ß-OH-BMIPP.



Scheme II.

Based upon the expected catabolism of fatty acids via the usual ß-oxidative pathway, the radioactive polar metabolite released from isolated rat hearts could represent ß-hydroxy BMIPP (ORNL/TM-xxxx). Availability of the authentic ß-OH-BMIPP has now provided an opportunity for chromatographic comparison with the unknown metabolite purified from the outflow of isolated Langendorff-perfused rat hearts after administration of [I-125]BMIPP (ORNL/TM-11014 and 11043). The results (Figure 2) clearly demonstrate that the metabolite is more polar than ß-OH-BMIPP. Further efforts are now being directed toward isolation of sufficient levels of the unknown metabolite for chemical and mass spectral analyses.

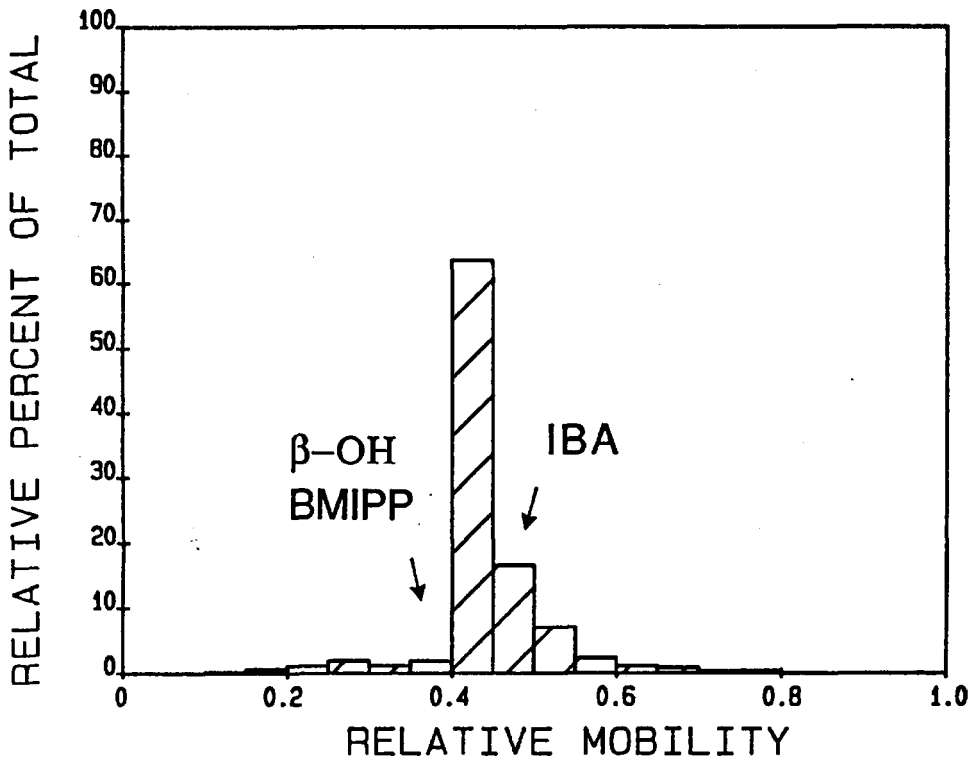


Figure 2. Thin-layer chromatogram (silica gel G; solvent benzene/dioxane/acetic acid, 80:18:2) of the unknown metabolite isolated from the perfusate of isolated rat hearts administered iodine-125-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP). (ß-OH=ß-hydroxy BMIPP; IBA = p-(iodophenyl)benzoic acid).

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2. DeGrado, T. R., Holden, J. E., Ng, C. K., Raffel, D. M., and Gatley, S. J. "β-Methyl-15-p-iodophenylpentadecanoic Acid Metabolism and Kinetics in the Isolated Rat Heart," Eur. J. Nucl. Med., 15, 78-80 (1989).

AGENTS FOR MEDICAL COOPERATIVES

One shipment of iodine-125-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) was shipped to Brookhaven National Laboratory (Dr. P. Som).

AGENTS PREPARED FOR COST-RECOVERY THROUGH THE ORNL ISOTOPES DISTRIBUTION OFFICE

Two shipments of Pt-195m were shipped to Beth Israel, Boston, Massachusetts (Dr. Kolodny), and one shipment each to the University of California, San Diego; the University of Utah, Salt Lake City; and the New York Medical Center, New York, New York (Dr. T. Reich).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Kubota, K., Som, P., Oster, Z. H., Brill, A. B., Goodman, M. M., Knapp, F. F., Jr., Atkins, H. L., and Sole, M. J. "Detection of Cardiomyopathy in an Animal Model Using Quantitative Autoradiography," J. Nucl. Med., 29, 1697-1703 (1988).

Srivastava, P. C., Robins, R. K., and Meyer, R. B., Jr. "Synthesis and Properties of Purine Nucleosides and Nucleotides," Chapter 2, pages 113-281, Vol. 1, Chemistry of Nucleosides and Nucleotides, L. B. Townsend, editor, Plenum Press, New York (1988).

Suggs, J. A., and Srivastava, P. C. "Synthesis and Biodistribution of p-Iodophenyl Analogues of a Natually Occurring Imidazole Ribonucleoside," J. Het. Chem., 25, 1331-1335 (1988).

Srivastava, P. C., Knapp, F. F., Jr., and Kabalka, G. W. "New Radiohalogenated Alkenyl Tellurium Fatty Acids," In, Proceedings of the Vth International Conference on the Chemistry of Selenium and Tellurium, Oak Ridge, TN, August 24-28, 1987; Published in, Phosphorus and Sulfur, 38, 49-58 (1988).

Patents

Goodman, M. M., and Knapp, F. F., Jr. "Radioiodinated Glucose Analogues for Use as Imaging Agents," U.S. Patent No. 4,7898,542, Patent Gazette, p. 290, December 6, 1988.

Miscellaneous

On October 5, F. F. Knapp, Jr., served on a doctoral thesis committee in the Cardiology Department at the Free University Hospital in Amsterdam, the Netherlands. He also presented a seminar in the Cardiology Department on October 6 and 7, in Liege, Belgium, to review recent results and coordinate clinical applications of the osmium-191/iridium-191m radionuclide generator system. He also helped organize a workshop in Liege, Belgium, to be held in January 1989.

A major U.S. radiopharmaceutical manufacturer, New England Nuclear/Dupont, has signed a licensing agreement with Martin Marietta Energy Systems, Inc. for the maleimide process for radioiodination of proteins. This is the first such licensing agreement for technology developed in the ORNL Nuclear Medicine Program. The technique was developed by P. C. Srivastava and shows promise for radiolabeling antibodies for both diagnostic and therapeutic applications. This concept of radiolabeling antibodies with radioactive iodine using the maleimide technology developed at ORNL is being used by scientists at Harvard Medical School and University of Southern California Medical School, who recently reported a modified radiochemical synthesis of this type of agent. The studies from these institutions were reported at a recent American Chemical Society meeting in Los Angeles and reported as a "Meeting Brief" in the October 10 issue of Chemical and Engineering News (page 321).

As part of the new OHER project entitled "Radioisotope Production and Development Technology," members of the Nuclear Medicine Program have assisted staff of the Chemical Technology Division on the purification procedures and gamma spectroscopy for Palladium-103 (Pd-103). The Pd-103 is an important radionuclide for therapy of prostatic carcinoma. Assistance has been provided in the development of methods for the final purification of Pd-103, which involves removal of zinc-65, iridium-192, and silver-110/111 impurities by ion-exchange chromatography.

F. F. Knapp, Jr., has accepted an appointment to serve as one of three members of the new U.S. editorial board of the nuclear medicine journal "NucCompact-European/American Communications in Nuclear Medicine." This journal, published in West Germany by GIT Verlag Ernst Giebeler, was established in 1970 as a mechanism for rapid publication of short communications in nuclear medicine and radiopharmaceutical development. It has been listed in "Current Contents" and "Excerpta Medica" since 1983. In order to further improve the quality of the journal and to stimulate wider authorship, the editorial board has been expanded to the United States.

Visitors

Robert Schenter, Ph.D., from Westinghouse at Hanford, Washington, visited the Nuclear Medicine Group on December 9 to discuss his calculations of expected production yields in various reactors of a variety of radionuclides of biomedical interest. These include xenon-127 for pulmonary ventilation studies, and tungsten-188 and osmium-194, which are parent radionuclides for generator systems. On December 13, Len Mausner, Ph.D., leader of the radioisotopes production team in the Medical Department at BNL, visited to discuss several projects of joint interest involving the production of radioisotopes of biomedical interest.

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47. H. J. Biersack, M.D., Director, Institut fur Klinische und Experimentelle Nuklear Medizin Der Universitat Bonn, Sigmund Freud Strasse 25, 5300 Bonn 1, West Germany
48. C. Brihaye, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
49. A. B. Brill, M.D., Ph.D., Commonwealth of Massachusetts, Univ. of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01605
50. T. F. Budinger, M.D., Donner Lab., LBL, Berkeley, CA 94720
51. W. Burr, M.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
52. P. Cho, OHER, U.S. DOE, MS-ER-73, Washington, D.C. 20545
53. D. W. Cole, Jr., U.S. DOE, ER-73, GTN, Washington, D.C. 20545
54. J. Crook, M.D., Ph.D., Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
55. S. J. DeNardo, M.D., Univ. California, Davis Medical Center, Sacramento, CA 95817
56. R. F. Dannals, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205
57. R. Dudczak, M.D., Dept. Nuclear Medicine, I. Medizinische Universitatsklinik, A-1090 Wien, Lazarettgasse 14, Vienna, Austria
58. J. Dunn, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
59. D. R. Elmaleh, Physics Research Dept., Massachusetts General Hospital, Boston, MA 02114
60. L. Feinendegen, Institut fur Medizin, Postfach 1913, D-5170, Julich 1, West Germany
61. A. Fritzberg, NeoRx Corporation, 410 West Harrison, Seattle, WA 98119
62. D. M. Goldenberg, M.D., Center of Molecular Medicine and Immunology, 1 Bruce Street, Newark, NJ 07103

63. M. Guillaume, Chef de Travaux, Centre de Recherches du Cyclotron, Universite de Liege, Belgium
64. D. R. Hamilton, Nuclear Medicine Branch, OTA/NCDRH/FDA, Rockville, MD 20857
65. C. J. Hardy, Chief, Isotope Division, Australian Nuclear Science and Technology Organization, Private Mail Bag 1, Menai, N.S.W. 2234, Australia
66. J. Hiltunen, Technical Research Centre of Finland, Reactor Laboratory, Otakaari 3 A, SF-02150 Espoo, Finland
67. K. Hubner, M.D., Department of Radiology, UT Memorial Hospital, Knoxville, TN 37920
68. K. J. Irgolic, Chemistry Dept., Texas A&M University, College Station, TX 77840
69. A. Jones, Dept. of Radiology, Harvard Medical School, Boston, MA 02115
70. G. Kirsch, Universite de Metz, Metz, France
71. J. Kropp, M.D., Institute for Clinical and Experimental Nuclear Medicine, University of Bonn, Bonn, West Germany
72. D. E. Kuhl, M.D., Division of Nuclear Medicine, University of Michigan Hospitals, University Hospital BIG 412/0028, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0028.
73. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
74. J. Logic, M.D., University of Alabama Medical Center, Birmingham, AL 35233
75. H.-J. Machulla, Institut fur Med. Strahlenphysik, Universitats-klinikum, Hufelandstrasse 55, D-4300, Essen 1, West Germany
76. J. N. Maddox, DOE-OHER, ER-73, Washington, DC 20545
77. D. Moody, Group INC-11, MS J-519, LASL, Los Alamos, NM 87545
78. Office of Assistant Manager for Energy Research and Development DOE-ORO, Oak Ridge, TN 37831
79. K. J. Panek, Mallinckrodt Diagnostica (Holland) B.V., Westerduinweg 3, P.O. Box 3, 1755 ZG Petten, Holland
80. R. Patterson, M.D., Nuclear Cardiology, Crawford Long Hospital, 550 Peachtree Street, NE, Atlanta, GA 30365-2225
81. C. L. Partain, M.D., Director, Medical Imaging Division, Vanderbilt University Medical Center, Nashville, TN 37232
82. R. C. Reba, M.D., George Washington Univ. Med. Center, Washington, DC 20037
83. S. N. Reske, M.D., Nuklear Medizin Abteilung, RWTH Aachen, Pauwelsstrasse 1, 5100 Aachen, West Germany
84. M. Robbins, Mallinckrodt, Inc., 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134
85. J. S. Robertson, DOE-OHER, ER-73/GTN, Washington, DC 20545
86. M. P. Sandler, M.D., Chief, Nuclear Medicine Section, Vanderbilt University Medical Center, Nashville, TN 37232
87. R. E. Schenter, Ph.D., Westington Hanford Co., Richland, WA 99352
88. F. Snyder, ORAU, Oak Ridge, TN 37831
89. P. Som, DVM, Medical Department, BNL, Upton, NY 11973
90. S. C. Srivastava, Bldg. 801, Medical Dept., BNL, Upton, NY 11973
91. A. Solomon, M.D., UT MRCH, Knoxville, TN 37920
92. H. W. Strauss, M.D., Nuclear Medicine Div., Massachusetts General Hospital, Boston, MA 02114

93-102. Office of Scientific and Technical Information, DOE, Oak Ridge, TN 37831

103. A. Vessey, Eastman Pharmaceuticals, 25 Great Valley Parkway, Great Valley, PA 19355
104. F. Visser, M.D., Cardiology Dept., Free University Hospital, De Boelelaan 117, Amsterdam, The Netherlands
105. H. N. Wagner, Jr., M.D., Div. of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 21205
106. L. C. Washburn, Medical and Health Sciences Division, ORAU, Oak Ridge, TN 37831
107. A. P. Wolf, BNL, Upton, NY 11973

108. D. V. Woo, Hahnemann University, Philadelphia, PA 19102
109. R. W. Wood, Jr., DOE-OHER, Washington, DC 20545
110. S. Wynchank, Research Institute for Medical Biophysics (RIMB), Republic of South Africa