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REPORT OF FOREIGN TRAVEL BY LEE C. WASHBURN, ORAU

Robert W. Wood, Director of Physical and Technological Research, ER-74, Headquarters, Germantown, Maryland

Attached is a copy of a trip report prepared by Lee C. Washburn covering his travel to Groningen, the Netherlands, during the period July 2-9, 1988. The traveler attended the Seventh International Symposium on Radiopharmaceutical Chemistry held July 4-8, 1988, and presented a paper entitled, "Synthesis of (^{18}F)7-Fluoroheptylamine and Tissue Distribution Studies in Rats."

The report has been reviewed and does not contain any classified information.

ORIGINAL SIGNED BY
M. C. WALLACE

for W. D. Adams, Director
Research and Waste Management Division

Attachment

cc w/atchmt:
J. F. Decker, ER-1, HQ, FORS
D. B. Waller, IE-1, HQ, FORS
J. G. Coyne, MA-28, OSTI
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COVER SHEET

FOR TRIP REPORTS SUBMITTED TO THE

OFFICE OF ENERGY RESEARCH

Destination(s) and Dates for
Which Trip Report Being Submitted: Groningen, The Netherlands July 2-9, 1988

Name of Traveler: Lee C. Washburn

Joint Trip Report /__/ Yes

/X/ No

If so, Name of Other Traveler(s): _____

_____

FOREIGN TRAVEL REPORT

July 2 - July 9, 1988

Lee C. Washburn, Ph. D.
Medical and Health Sciences Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37831-0117

Prepared July 27, 1988

SUMMARY

(1) Traveler: Lee C. Washburn, Scientist, Radiopharmaceutical Development and Preclinical Nuclear Medicine, Medical and Health Sciences Division, Oak Ridge Associated Universities (Contract Number DE-AC05-76OR00033), Oak Ridge, Tennessee 37831-0117. This trip report is dated July 27, 1988.

(2) Destination: Groningen, The Netherlands. The trip covered the period July 2-9, 1988. Official business was involved during the period July 4-8.

(3) Purpose of Trip: To attend the Seventh International Symposium on Radiopharmaceutical Chemistry, held July 4-8, 1988, in Groningen, The Netherlands, and present in an oral session a paper entitled "Synthesis of [^{18}F]7-Fluoroheptylamine and Tissue Distribution Studies in Rats".

(4) Abstract: The Seventh International Symposium on Radiopharmaceutical Chemistry attracted a total of 325 participants representing 21 countries. A total of five invited review lectures, 81 proffered oral papers, and 132 poster presentations were given during the 4-1/2 day symposium. There were 15 scientific sessions of which eight dealt with ^{11}C- and/or ^{18}F-labeled radiopharmaceuticals. The meeting was quite well organized and well attended, and the papers were generally of high quality. Several noteworthy advances in radiopharmaceutical chemistry were reported.

(5) Cost of Travel: The total cost of this trip was approximately $2128.94. (The exact cost will vary slightly from this value because of uncertainty at this time as to the exchange rate to be used for the final cost computation.) The entire cost was charged to DOE Budget Activity HA 02 07 01 for the Radiopharmaceutical Development and Preclinical Nuclear Medicine Program.

COMPREHENSIVE REPORT

This trip began when I left my home in Oak Ridge, Tennessee at 10:00 a.m. on Saturday, July 2, 1988. I traveled from Knoxville to Pittsburgh and then on to New York's Kennedy International Airport via U. S. Air and then flew to Amsterdam on TWA flight number 814. I arrived on schedule in Amsterdam at 9:40 a.m. on Sunday, July 3, 1988. This flight was very popular for U. S. scientists traveling to the symposium in Groningen. Probably 30-40 of the passengers were meeting participants.

I was met at Amsterdam's Schiphol Airport by a cousin and her husband, Shelley and S. A. Evans, who live in Leusden, about 25 miles east of Amsterdam, near the city of Amersfoort. S. A. Evans is a U. S. serviceman stationed at Soesterberg Air Force Base. They took me by car to their home, where we visited for a few hours and had lunch. They then took me to the train station in Amersfoort, where I boarded a train bound for Groningen. I arrived in Groningen at 4:15 p.m. (Amersfoort is on the direct train route from Amsterdam to Groningen) and took a bus from the train station to the Martinihal Centrum, or Congress Center, where the Seventh International Symposium on Radiopharmaceutical Chemistry was held. This facility proved to be very well suited as a site for the meeting. After picking up my registration materials, I stayed for a while at the informal reception held on Sunday evening for meeting participants and then retired to my hotel. I was very fortunate in being assigned to the Altea Hotel, a very modern hotel located immediately adjacent to the Martinihal Centrum. Many other participants were assigned to quite distant hotels, one of which was located in the town of Haarlem, which is 8-10 miles from Groningen, and had to travel to and from the meeting site by public transit.

The symposium officially began at 9:15 a.m. on Monday, July 4, 1988, with a welcome and opening remarks by Dr. Willem Vaalburg, of the University Hospital in Groningen, chairman of the Local Organizing Committee for the symposium. Each of the seven biannual symposia have been "hosted" by a different member of the International Founding and Organizing Committee. Professor Dr. J. M. Minderhoud, Dean of the Faculty of Medicine of the University of Groningen, gave the official welcome for the university, followed by an invited lecture by Dr. W. G. J. Hol of the University of Groningen's Department of Chemistry. This lecture, on the subject "Protein Crystallography, Molecular Modelling and Rational Drug Design", although not dealing with subject matter typically presented at a meeting on radiopharmaceutical chemistry, proved to be very interesting and worthwhile. Dr. Hol discussed how to use protein x-ray crystallography and computer modeling to design a drug which will fit a protein binding site on a foreign organism, thus killing it, without binding to analogous proteins of the host organism. The primary example presented was Dr. Hol's work on development of useful drugs for treatment of sleeping sickness, one of the six most important tropical diseases, according to the World Health Organization. Sleeping sickness affects approximately one-half of the continent of Africa, killing both people and cattle. The disease is carried by a mosquito called T. brucei. A number of enzyme proteins have been isolated from T. brucei and purified as crystals, and their x-ray crystallographic structures have been determined. This information is being used to design new drugs for sleeping sickness. Implications abound as to how

this sort of x-ray crystallographic/computer modeling approach could be used as a means of more rationally designing new radiopharmaceutical agents.

In the remaining 4-1/2 days of the symposium, four additional invited review lectures were presented on various topics of interest to researchers in the field of radiopharmaceutical chemistry. In addition, a total of 213 proffered papers were presented, 81 as oral presentations and the other 132 as posters. I shall attempt to give my personal interpretation of the trends that emerged at this meeting and to briefly discuss a few papers that were of special interest to me.

First, on the basis of both the number of participants (325, representing a total of 21 countries) and the number of presentations (as stated above), it is evident that research in the field of radiopharmaceutical chemistry continues to grow and fluorish. It has been my privilege to attend all except one of the seven symposia in this series including the first one held at Brookhaven National Laboratory in 1976, which drew perhaps 75-100 participants. Each symposium I have attended has seemed to be bigger and better than the previous one, which to me is evidence of both tremendous progress and increasing interest in radiopharmaceutical chemistry.

A second very noticeable trend has to do with the subject matter of the symposium. In the early symposia in this series, papers dealing with radiopharmaceuticals for positron emission tomography (PET) were greatly in the minority. At this symposium, out of a total of 15 sessions, eight dealt with ^{11}C- and/or ^{18}F-labeled radiopharmaceuticals. Particularly emphasized was work on high-specific-activity ^{11}C- and ^{18}F-labeled ligands for PET receptor density studies. Of the remaining seven sessions, three dealt with technetium-99m chemistry, one with radionuclide production and targetry, one with heavy halogens, one with indium/gallium, and one with proteins/antibodies. It was surprising to me that so few papers were presented in the area of radiolabeled monoclonal antibodies, considering the great interest in this field in recent years, including a great number of papers at the recent meeting of the Society of Nuclear Medicine in San Francisco. However, I believe that the paucity of papers in this area reflects the movement of this research into the clinical arena, as opposed to continuing emphasis on development of new monoclonal antibody radiolabeling methodology. I am not sure that such a shift in emphasis at this point is wise.

Three of the four invited review papers were of particular interest to me. Dr. Joanna Fowler of Brookhaven National Laboratory did a good job of reviewing the chemistry of ^{18}F-labeled radiopharmaceuticals, as she has previously done in a number of other meetings I have attended. She is very adept at emphasizing recent developments, so her presentations are always up to date. Her review would have been more effective, however, if it had been scheduled near the end of the meeting, instead of near the beginning, so that it could have served more effectively as a summary of the great number of fluorine-18 papers presented, which is really what it was. Dr. John Clarke of Hammersmith Hospital (London, England) gave an excellent review of remote controlled and automated radiopharmaceutical synthesis, discussing both the hardware available for such work and also the thought processes that should go into choosing which type of hardware is appropriate for a particular application. Dr. Ken Krohn of

the University of Washington reviewed the pharmacokinetics of receptor-based radiopharmaceuticals, particularly the physical chemistry of ligand-receptor interactions.

One of the most interesting proffered papers was given by Dr. P. Bjurling of the University of Uppsala (Sweden) on a multi-enzymatic synthesis of some ^{11}C-labeled amino acids with roles as neurotransmitter precursors - tyrosine, 3,4-dihydroxyphenylalanine (DOPA), tryptophan, and 5-hydroxytryptophan. The precursor for each of these ^{11}C-labeled amino acids is D,L-[3-^{11}C]alanine, obtained by direct alkylation with $^{11}CH_3I$. Then, using a relatively simple one-pot procedure, a mixture of enzymes is used to convert this simple amino acid via ^{11}C-labeled pyruvic acid to the ^{11}C-labeled neurotransmitter precursor of interest. One can select the amino acid to be made by simple changes in the reaction precursors and enzyme mixture. These researchers have achieved 10-30% radiochemical yields of the enantiomerically pure 3-^{11}C-labeled L-amino acids in a total synthesis time of 50 minutes from $^{11}CO_2$.

In the area of radiolabeled monoclonal antibodies, which is especially relevant to our research, an interesting paper was given by Dr. S. Mirzadeh of the NIH, who showed that the biodistributions of similarly prepared ^{90}Y-labeled and ^{111}In-labeled monoclonal antibody B72.3 are quite different, especially for bone uptake. These results illustrate the problems in using data for an ^{111}In-labeled monoclonal antibody to predict the radiation dosimetry (especially for bone marrow, the critical organ) of the analogous ^{90}Y-labeled monoclonal antibody.

Paik and co-workers of George Washington University Medical Center compared the biodistribution effect of introducing a diester linkage between a monoclonal antibody and DTPA as compared to the more common thiourea linkage. They found that the ^{111}In-labeled antibody conjugates containing diester and thiourea linkages were retained similarly in the lung (target) and in normal organs such as liver and kidneys, but that the blood clearance was much faster for the diester conjugate. This is a potential advantage for the imaging of tumors in blood-rich regions.

Papers on radiohalogenated monoclonal antibodies emphasized the introduction of the radiohalogen in a form so that it is stabilized on a nonactivated aromatic ring as opposed to the more traditional electrophilic radiohalogenation on the tyrosine moieties of proteins, with which there is a pronounced tendency to dehalogenate in vivo. Dr. Michael Zalutsky of Duke University and Dr. D. Scott Wilbur of NeoRx Corporation presented similar papers dealing with radiohalogenation of N-succinimidyl tri-n-butylstannyl benzoate followed by reaction of the resulting radioactive N-succinimidyl intermediate with the epsilon-amino groups on an antibody's lysine residues. Zalutsky says that the meta-isomer of N-succinimidyl tri-n-butylstannyl benzoate works best, whereas Wilbur uses the para-isomer. The reaction works quite well for astatine-211 (an alpha-emitting radionuclide with potential for radiotherapy of cancer) and bromine-77, as well as for the radionuclides of iodine. Dr. P. C. Srivastava of Oak Ridge National Laboratory reported on use of N-(p-[^{125}I]iodophenyl)maleimide for labeling monoclonal antibodies, again with the radioiodine stabilized on a phenyl ring, and Dr. C.-Y. Shiue of Brookhaven National Laboratory reported a similar reagent for radiolabeling with fluorine-18.

Some interesting new radiolabeled receptor ligands reported on at this meeting included the following: [^{11}C]N-methylketanserin for serotonin S_2 receptor imaging (Dannals, Johns Hopkins); ^{11}C-labeled (+)2H-tropanil benzilate (TRB) and N-methyl-4-piperidyl benzilate (NMPB) for muscarinic receptor imaging (Mulholland, University of Michigan); and radioiodinated N-alkyl 2'-iodospiperone derivatives for dopamine receptor imaging (Saji, Kyoto University). Dr. Sharon Stone-Elander of Karolinska Hospital (Stockholm, Sweden) reported the production of [isopropyl-^{11}C]nimodipine, a calcium channel antagonist. This agent was taken up by the visual cortex and thalamus within the first 15 minutes after injection and uptake was blocked by administration of the stable drug.

Among the interesting new chemistry information coming from this meeting was the finding reported by Dr. T. J. de Groot of the host institution (University Hospital, Groningen, The Netherlands) that the specific activity of 16α-ethyl-21-(^{18}F) fluoro-19-norprogesterone, a potential ligand for progesterone receptor imaging, was increased by a factor of four via use of potassium phosphate as the counter cation in the Kryptofix 222-assisted nucleophilic displacement of [^{18}F]fluoride instead of the usual potassium carbonate. The reason for this effect is not known at this time. Also of interest was the report of Dr. Hank Kung (University of Pennsylvania) concerning the advantageous use of peracetic acid as an oxidizing agent in the preparation of radioiodinated iodobenzamide (IBZM), a phenolic compound with affinity for dopamine receptor sites. Dr. G. Engelskirchen (Institut fur Chemie, KFA Julich, FRG) presented optimization studies of the aminopolyether-supported nucleophilic [^{18}F]2-fluoro-2-deoxyglucose synthesis.

A potentially important new development that seems to be emerging in radiopharmaceutical chemistry is the use of polymeric supports for synthesis. Several pioneering reports in this area were made at this symposium. For example, Dr. George Kabalka (University of Tennessee) reported on use of polymeric organoboranes for the preparation of both [^{15}O]butanol and [^{13}N]butylamine and Dr. G. K. Mulholland (University of Michigan) reported preliminary results on the use of polymeric quaternary ammonium hydroxide resins for both trapping and nucleophilic activation of [^{18}F]fluoride and [^{11}C]cyanide.

My paper, entitled "Synthesis of [^{18}F]7-Fluoroheptylamine and Tissue Distribution Studies in Rats" (attached as Appendix A), was presented orally in the final session on Tuesday, July 5. The paper seemed to be well received, with a number of questions following the talk dealing with the synthesis and potential application of this agent.

The symposium gave me the opportunity to consult with a number of scientists about various aspects of our research at ORAU Medical and Health Sciences Division. For example, I talked with Dr. Ron Finn of the NIH Cyclotron Facility about the schedule for our obtaining future batches of [^{18}F]fluoride and with Dr. Finn, Dr. Alfred Wolf and Dr. David Schlyer of Brookhaven National Laboratory, and Dr. Tom Ruth of TRIUMF, Vancouver, British Columbia, Canada concerning the suitability of the 95% nitrogen - 5% hydrogen gas target for making $^{11}CH_4$ (as a precursor to H^{11}CN) with the ORBIT, Inc. 8 MeV cyclotron, which was recently installed at ORAU Medical and Health Sciences Division.

The symposium concluded with closing remarks by Dr. Vaalburg and Dr. William C. Eckelman of the Squibb Institute for Medical Research, New Brunswick, New Jersey. Dr. Eckelman is to be the Chairman of the Local Organizing

Committee for the Eighth International Symposium on Radiopharmaceutical Chemistry, to be held June 24-29, 1990, at Princeton, New Jersey,

Following the conclusion of the symposium at 12:15 p.m. on Friday, July 8, I traveled by train from Groningen to Amersfoort, where I was met at the train station by S. A. Evans, my cousin's husband. I spent the night at their apartment in Leusden. On Saturday, July 9, my relatives took me to Amsterdam's Schiphol Airport for my return flight to the U. S., TWA's flight number 815 to Kennedy International Airport in New York. I then traveled on TWA to Pittsburgh, where I connected with a U. S. Air flight to Knoxville. I returned to my home in Oak Ridge at approximately 11:00 p.m. on Saturday, July 9.

EVALUATION

I feel that the Seventh International Symposium on Radiopharmaceutical Chemistry in Groningen, The Netherlands was a well-organized and very successful meeting. The symposium was quite well attended, with 325 participants representing 21 countries. The papers were of generally high quality, and several noteworthy advances were reported. The meeting was very valuable to me as a radiopharmaceutical chemist, because I was able to keep abreast of the new research taking place in this area. I also had the opportunity to consult with several renowned scientists on topics of interest to ORAU's research efforts.

APPENDICES

A copy of my paper, entitled "Synthesis of [^{18}F]7-Fluoroheptylamine and Tissue Distribution Studies in Rats," is attached as Appendix A. (The papers are generally written up as "long abstracts" of about 2-3 pages in length, which provides more details than the typical abstract for a scientific meeting.) A copy of the entire scientific program for the Seventh International Symposium on Radiopharmaceutical Chemistry is attached as Appendix B. I was supplied with a book of proceedings for the symposium which will be published in a later issue of the Journal of Labelled Compounds and Radiopharmaceuticals.

APPENDIX A

paper 99

SYNTHESIS OF [^{18}F]7-FLUOROHEPTYLAMINE AND TISSUE DISTRIBUTION STUDIES IN RATS

L.C. Washburn, T.T.H. Sun, B.L. Byrd, and J.E. Crook
Medical and Health Sciences Division, Oak Ridge Associated Universities,
Oak Ridge, TN 37831

^{11}C-Labeled primary aliphatic amines with chain lengths of four to 13 carbon atoms are localized rapidly and selectively by lung endothelial cells (1), which makes these agents potentially useful for PET pulmonary function studies. However, because such amines are rapidly catabolized in vivo with loss of radiolabel (Fig. 1), quantitation of pulmonary uptake is difficult.

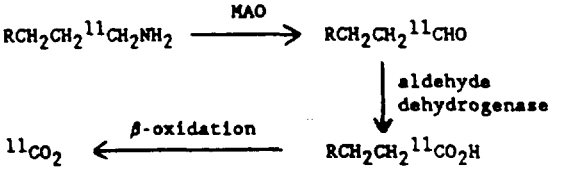


Figure 1. Metabolism of ^{11}C-labeled primary aliphatic amines.

We have previously studied the effects of various structural modifications, i.e., chain branching at the 2- and 3-positions, use of a bulky t-butyl substituent at the 2-position, and elongation of the straight carbon chain, on the uptake and retention of ^{14}C-labeled primary aliphatic amines in rat lung (2,3). Only chain elongation greatly affected the lung residence time of primary aliphatic amines. ^{14}C-Labeled octadecylamine demonstrated rapid and selective lung uptake and, unlike smaller amines, was not metabolically lost from rat lung within the first 30 min after intravenous administration (4). Furthermore, differential lung uptake between the normal and irradiated lungs was observed in rats receiving large-dose (5000 rads) unilateral irradiation of the thorax (4). A potential hindrance to use of ^{11}C-labeled octadecylamine, however, is its water insolubility. For the biodistribution studies in rats, 3% aqueous human serum albumin was used to effect solubilization (4).

The present paper describes an alternate approach to the development of a primary aliphatic amine labeled with a positron-emitting radionuclide for use in PET pulmonary function studies. We theorized that ^{18}F-labeled ω-fluorine-substituted primary aliphatic amines might be resistant to metabolic loss of radiolabel from the lung because the position of the radionuclide would be distal to the site of catabolism. This paper describes the synthesis and rat biodistribution studies of a model compound, [^{18}F]7-fluoroheptylamine (IV).

The synthetic route to IV is shown in Fig. 2. Commercially available 7-bromoheptanenitrile (I) was converted to 7-iodoheptanenitrile (II) in 40% yield by treatment with sodium iodide in acetone at room temperature for 24 hr. II was used as a substrate for nucleophilic displacement with [^{18}F]fluoride. The ^{18}O-enriched water (0.5 ml) was removed from [^{18}F]fluoride by azeotropic distillation with acetonitrile in the presence of tetraethylammonium hydroxide (50 μl of 20% aqueous solution) and tetraethylammonium fluoride hydrate (50 mg, 0.3 mmole). A solution of II (50 μl, ~70 mg, 0.3 mmole) in acetonitrile (1.0 ml) was added, and the mixture was heated in a sealed 3-ml stainless steel reaction vessel at 190°C for 30 min. The vessel was cooled, and the contents were withdrawn into a glass test tube, where the acetonitrile was evaporated by means of a stream of nitrogen gas. The mixture was extracted with ether and dried over anhydrous sodium sulfate for 15 min. The ether solution (~2 ml) containing III was added by means of a syringe to a glass test tube (fitted with a rubber septum) containing lithium aluminum hydride (1.0 ml of a 1 M solution in ether) and anhydrous ether (1.0 ml). The mixture was stirred magnetically at room temperature for 30 min. The reaction was quenched by addition of water, and

15% aqueous sodium tartrate (2.0 ml) was added to hydrolyze aluminum complexes. The two-phase mixture was separated and extracted with ether, the combined ether extracts were filtered, and the ether was evaporated. The residue was dissolved in 80 μl of the HPLC mobile phase (methanol/water/acetic acid, 4:6:1 by volume) and injected onto the HPLC. The mixture was separated by HPLC using a 4.6 mm x 25 cm Ultrasphere ODS, 5 μ HPLC column and a flow rate of 0.5 ml/min. Elution was monitored using a refractive index detector and a custom liquid-column single channel analyzer radioactivity detector, connected in series. IV, seen in corresponding peaks on both detectors, eluted in approximately 7 min and was collected in a volume of ~1 ml. After addition of 100 μl of 1 M hydrochloric acid to protonate the amine, the solvent was evaporated using a 95°C hot plate and a stream of nitrogen gas, and the residue was dissolved in 0.9% saline for injection (12 ml).

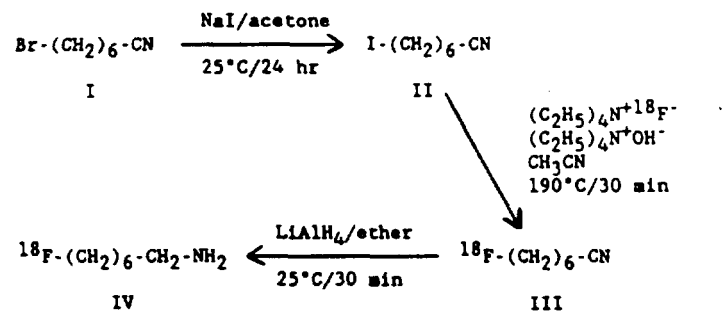


Figure 2. Synthetic route to [^{18}F]7-fluoroheptylamine.

The overall two-step radiochemical yield, corrected for decay, was 6%. This yield has not been optimized and the low yield can in part be attributed to losses in the various solvent evaporation steps because of the pronounced volatilities of both III and IV.

The saline solution of IV was administered intravenously to male three-month-old Fischer 344 rats for tissue distribution studies. Animals were sacrificed at 1, 5, 20, and 60 min after injection. The results, expressed as percent of the injected dose per gram and normalized to a body weight of 250 g, are shown in Table 1.

TABLE 1. Tissue Distribution of [^{18}F]7-Fluoroheptylamine in Male Fischer 344 Rats.

	Percent/g/250 g			
Tissue	1 Min	5 Min	20 Min	60 Min
Lung	3.06 ± 0.19*	1.39 ± 0.05	0.50 ± 0.03	0.11 ± 0.01
Liver	1.14 ± 0.14	1.86 ± 0.08	0.96 ± 0.09	0.15 ± 0.01
Spleen	0.78 ± 0.08	0.98 ± 0.02	0.42 ± 0.03	0.08 ± 0.01
Kidney	6.48 ± 0.26	3.82 ± 0.12	1.32 ± 0.11	0.18 ± 0.06
Muscle	0.39 ± 0.04	0.33 ± 0.02	0.15 ± 0.01	0.04 ± 0.01
Heart	0.98 ± 0.06	0.66 ± 0.01	0.32 ± 0.02	0.05 ± 0.01
Blood	0.37 ± 0.02	0.49 ± 0.03	0.38 ± 0.03	0.05 ± 0.01

*Mean of five animals ± S.E.

These preliminary experiments suggest that the radiolabel is lost from the lung and other tissues with [^{18}F]7-fluoroheptylamine in similar amounts and time frame as in previous studies with ^{11}C-labeled primary aliphatic amines of the same approximate size. The biodistribution in the New England Deaconess Hospital (NEDH) rat, an unusual animal model that spontaneously becomes hypertensive and also has a high incidence of catecholamine-producing pheochromocytomas (5), was similar. Larger amines in the series of ^{18}F-labeled ω-fluorine-substituted primary aliphatic amines, analogous to ^{11}C-labeled octadecylamine, would likely show more favorable lung uptake and retention properties than the model compound studied here. Development of synthetic routes to such compounds is in progress.

This article is based on work supported by contract number DE-AC05-76OR00033 between the U. S. Department of Energy and ORAU. The authors thank Dr. R. D. Finn of the Cyclotron Facility, National Institutes of Health, Bathesda, Md., for supplying the [^{18}F]fluoride used in this study.

1. Fowler, J.S., Gallagher, B.M., MacGregor, R.R., and Wolf, A.P., Pharmacol. Exp. Ther., 198, 133 (1976).

2. Washburn, L.C., Sun, T.T., Byrd, B.L., and Kabalka, G.W., J. Labelled Comp. Radiopharm., 19, 1282 (1982).

3. Washburn, L.C., Wallace, R.T., Byrd, B.L., and Sun, T.T., Clin. Nucl. Med. 8, P60 (1983).

4. Washburn, L.C., Wallace, R.T., Byrd, B.L., Sun, T.T., Coffey, J.L., and Hubner, K.F., J. Nucl. Med., 25, P126 (1984).

5. Warren, S. and Chute, R.N., Cancer, 29, 327 (1972).

APPENDIX B

MONDAY 4 JULY

0930 OPENING REMARKS: Willem Vaalburg, Chairman

0945 OPENING LECTURE
PROTEIN CRYSTALLOGRAPHY, MOLECULAR MODELLING AND RATIONAL DRUGS DESIGN
W. G. J. Hol, Department of Chemistry, University of Groningen

SESSION A: FLUORINE-18 CHEMISTRY I

1100-1300 Chairman: Alfred P. Wolf

Invited Lecture
FLUORINE-18 LABELED RADIOTRACERS FOR PET: METHODS AND PROBLEMS
Joannna S. Fowler, Brookhaven National Laboratory, Upton, New York

POSTERS IN SESSION A

SESSION B: TECHNETIUM CHEMISTRY AND LABELLED COMPOUNDS

1400-1515 Chairman: Alun G. Jones

POSTERS IN SESSION B

SESSION C: CARBON-11 AND NITROGEN-13 CHEMISTRY

1545-1715 Chairman: Michael J. Welch

POSTERS IN SESSION C

TUESDAY 5 JULY

SESSION D: HEAVY HALOGENS

0900-10.30 Chairman: David J. Silvester

POSTERS IN SESSION D

SESSION E: RADIONUCLIDE PRODUCTION AND TARGETTING

1115-1300 Chairman: Anne M. J. Paans

POSTERS IN SESSION E

SESSION F: CARBON-11 LABELLED RECEPTOR LIGANDS

1400-1515 Chairman: Dominique Comar

POSTERS IN SESSION F

SESSION G: FLUORINE-18 CHEMISTRY

1600-1715 Chairman: Gerhard Stöcklin

POSTERS IN SESSION G

WEDNESDAY 6 JULY

SESSION H: CARBON-11 CHEMISTRY

0900-1030 Chairman: Tatsuo Ido

Invited Lecture
REMOTE CONTROLLED AND AUTOMATED CHEMICAL SYNTHESIS
John C. Clarke, Hammersmith Hospital, London

107. PROBING THE BIOCHEMICAL BASIS OF THE PET IMAGE. MECHANISTIC PET STUDIES OF [^{11}C]L-DEPRENYL BINDING USING THE DEUTERIUM ISOTOPE EFFECT
J. S. Fowler, A. P. Wolf, R. R. MacGregor, S. L. Dewey, J. Logan, D. Schlyer, B. Långström 236

108. SYNTHESIS OF [^{11}C]SODIUM THIOCYANATE AND (ISOPROPYL-^{11}C)

SESSION I: TECHNETIUM CHEMISTRY

1100-1300 Chairman: Akira Yokoyama

Invited Lecture
NEW ASPECTS OF TECHNETIUM CHEMISTRY
Alun G. Jones, Harvard Medical School, Boston

POSTERS IN SESSION I

THURSDAY 7 JULY

SESSION J: PROTEINS AND ANTIBODIES

0900-1015 Chairman: William C. Eckelman

POSTERS IN SESSION J

SESSION K: FLUORINE-18 CHEMISTRY

1100-1300 Chairman: Heinz H. Coenen

POSTERS IN SESSION K

SESSION L: INDIUM AND GALLIUM

1400-1515 Chairman: Monte Blau

POSTERS IN SESSION L

SESSION M: CARBON-11 AND FLUORINE-18-LABELLED COMPOUNDS

1545-1700 *Chairman: Bengt Långström*

POSTERS IN SESSION M

FRIDAY 8 JULY

SESSION N: TECHNETIUM CHEMISTRY

0900-1030 Chairman: Wolfgang Maier-Borst

POSTERS IN SESSION N

SESSION O: FLUORINE-18 CHEMISTRY

1100-1200 Chairman: Sharon Stone-Elander

POSTERS IN SESSION O

POSTERS IN SESSION P

William C. Eckelman, Chairman
8th International Symposium on Radiopharmaceutical Chemistry
New Brunswick, USA, 1990.

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Executive
Office

August 2, 1988

Mr. William D. Adams, Director
Research and Waste Management Division
Department of Energy
Oak Ridge, Tennessee 37831

Subject: TRANSMITTAL OF FOREIGN TRIP REPORT
Dr. Lee C. Washburn - GRONINGEN, THE NETHERLANDS

Dear Mr. Adams:

Seven copies of the subject report are enclosed. This report does not contain any proprietary data.

Sincerely yours,

Jon M. Veigel
Executive Director

BAKER

Enclosures

DOE F 1325.8
(12-84)

United States Government **Department of Energy**

memorandum

DATE: JUL 07 1988

REPLY TO ATTN OF: ER-622

SUBJECT: Approved 1512.1's

TO: Margie Wallace, ER-122
Agreement Administrative Specialist
Oak Ridge Operations Office

Please find attached approved 1512.1's for the foreign travel of the following individuals:

Dommett, David W. - Brisbane Grammar School
Dommett, Thomas W. - Queensland Food Res. Lab.
Lacsamana, Ariel B. - Manila Sci. High School
Malloraca, Marlow A. - Manila Sci. High School
Mougey, Jean - CEBAF
Walecka, J. Dirk - CEBAF
Washburn, Lee C. - ORAU

A trip report is required from each traveler upon completion of his/her travel. If the travel was cancelled or revised in any way, please advise us.

Robert L. Main
Office of Management
Office of Energy Research

Attachment(s)

1128257

7/15/88 cy of approved 1512.1 to Carol Kates, ORAU/aa 1515 ORAU

X-393

DOE F 1512.1
(8/88)

All Other Editions Are Obsolete

U.S. DEPARTMENT OF ENERGY

REQUEST FOR APPROVAL OFFICIAL FOREIGN TRAVEL

OMB Control No.
1910-2100

PART A—SUMMARY TRAVEL INFORMATION

ORGANIZATION: OAK RIDGE ASSOCIATED UNIVERSITIES

STI FAXED TO IE-1,
4-25-88

COST TO DOE: $2732.00

FUND SOURCE: HA 02 07 01 0

NAME OF TRAVELER: LEE C. WASHBURN

DOE/CONTRACTOR/UNIVERSITY: C

DESTINATION: Groningen, The Netherlands

DATES: 07/03/88 TO 07/08/88

PURPOSE: To attend the Seventh International Symposium on Radiopharmaceutical Chemistry. Will present paper entitled, "Synthesis of [^{18}F]7-Fluoroheptylamine and Tissue Distribution Studies in Rats".

AGREEMENT: NONE

DESTINATION: ____

DATES: __/__/__ TO __/__/__

PURPOSE: ____

AGREEMENT: ____

DESTINATION: ____

DATES: __/__/__ TO __/__/__

PURPOSE: ____

AGREEMENT: ____

DESTINATION: ____

DATES: __/__/__ TO __/__/__

PURPOSE: ____

AGREEMENT: ____

1128256

DOE F 1512.1
(8-89)

U.S. DEPARTMENT OF ENERGY

OMB Control No
1910-2100

REQUEST FOR APPROVAL OFFICIAL FOREIGN TRAVEL

(Previous Editions are Obsolete)

PART B—To be completed by traveler's administrative officer

Budget and Reporting Classification to be charged: HA 02 07 01 0
(see Chapter II, Accounting Practices and Procedures Handbook)

PART C—To be completed by traveler

1a. NAME OF TRAVELER Lee C. Washburn	c. DATE AND PLACE OF BIRTH [redacted], Kentucky, U.S.A. [redacted]
b. CITIZENSHIP U.S.	d. PASSPORT NUMBER *(If available)*
2a. HOME ADDRESS [redacted]	b. BUSINESS ADDRESS P. O. Box 117 (FTS Tel: 626-3099) Oak Ridge, TN 37831-0117 c. TELEPHONE NUMBER
3a. EMPLOYER Oak Ridge Associated Universities	c. CONTRACT NUMBER US DOE DE-AC05-76OR00033
b. ORGANIZATIONAL UNIT Medical and Health Sciences Division	d. POSITION TITLE *(Including profession)* Scientist, Radiopharmaceutical Development and Preclinical Nuclear Medicine

4. PURPOSE OF TRAVEL—Include all pertinent background information leading to travel and attach copies of invitations and correspondence regarding travel to present papers, give speeches, or to attend conference or symposia. Justification for travel must be provided including benefit to be derived by the government if trip is taken. Also identify by name and organization other DOE and contractor personnel who, to the traveler's knowledge, are going to the same destination at the same time as the traveler. In addition, specify nature and classification of information to be disclosed including titles of papers to be presented; nature of information to be obtained at each of the places to be visited and conferences to be attended and its relation to traveler's work. Travelers are responsible for obtaining clearances for papers or speeches when necessary. If more space is required, attach a separate sheet. NOTE: IF THIS INFORMATION IS CLASSIFIED BE SURE TO CLASSIFY THIS FORM APPROPRIATELY.

The purpose of this travel is to attend the Seventh International Symposium on Radiopharmaceutical Chemistry, and present paper entitled, "Synthesis of [^{18}F]7-Fluoro-heptylamine and Tissue Distribution Studies in Rats".

Attached are copies of pertinent information regarding this biannual international symposium which is probably the most important single forum for the communication of new advances in radiopharmaceutical chemistry. As a researcher in this field, it is very important that I have the opportunity to attend this meeting both to share our research results with others and to learn new methods that will be useful in our future research. At this time I do not know what other DOE and contractor personnel will be attending the meeting. However, no other personnel from Oak Ridge Associated Universities will attend.

0622211

X-1946

Privacy Act Information Statement. Collection of the information is authorized by the Department of Energy Organization Act of 1977, P.L. 95-91. Disclosure of the personal information requested is mandatory to support authorization for official travel to foreign countries, and to obtain a passport. The information furnished will be used by DOE to authorize travel and payment of travel expenses; by the Department of State to issue a passport; and by the General Accounting Office to audit and verify the accuracy and legality of disbursements.

shall be indicated. NOTE: IF INFORMATION IS CLASSIFIED, CLASSIFY THIS FORM APPROPRIATELY.)

DATES	LOCATION (Installation, City, Country)	INDIVIDUALS TO BE CONTACTED	SUBJECTS OF DISCUSSION	(Check One) Classified	Unclassified
07/03/88	Oak Ridge-Groningen, The Netherlands				X
07/03/88	Arrive Groningen, The Netherlands		To attend the Seventh International Symposium on Radiopharmaceutical Chemistry, and present paper, "Synthesis of [^{18}F]7-Fluoroheptylamine and Tissue Distribution Studies in Rats".		X
07/04/88	Attending meeting				
07/05/88	Attending meeting				
07/06/88	Attending meeting				
07/07/88	attending meeting				
07/08/88	Leave Groningen, The Netherlands				X
07/08/88	Arrive Oak Ridge, TN				X

6. HAS TRAVELER SUBMITTED DOE FORM 1812.2 TO COGNIZANT DOE SECURITY OFFICE? *(Required for travel to a sensitive country by an individual who currently holds or has ever held, within the last 5 years, a DOE Access Authorization.)*

☐ YES ☒ NO: Have not held a DOE Access Authorization within last 5 years

7. SIGNATURE OF TRAVELER—By signing, the traveler acknowledges the obligation to file a trip report within 30 days of return to duty station.

Lee C. Washburn — *(Signature)* 03/28/88 — *(Date)*

PART D—To be completed by official responsible for travel funds

8a. ESTIMATED COST OF TRAVEL TO DOE (Airfare $1,914 train, taxi,etc)

Transportation	$ 2030.00
Per Diem and Miscellaneous	$ 702.00
Total	$ 2732.00

b. IF PART OF COST OF TRAVEL IS TO BE PAID OR HAS BEEN REQUESTED FROM SOURCES OTHER THAN DOE, INDICATE SOURCE AND AMOUNT.

N/A

TRAVEL FUNDS ARE NOW AVAILABLE FOR THIS TRIP

Billie P. Ryan 3/29/88 — Division Business Office *(Signature and Title)* (Date)

William F. Countiss 4/11/88 — William F. Countiss, Manager of Finance (Date)

PART E—To be completed by Traveler's supervisor

9. REVIEW AND COMMENTS:

William W. Lewis 3/29/88 — Division Chairman *(Signature and Title of Supervisor)* (Date)

William E. Felling 4/11/88 — William E. Felling, Executive Director (Date)

PART F—To be completed at DOE Field Organization

10. NON SENSITIVE TRAVEL: Review/approval by Head of DOE Field Organization. *(Approval may be given if such authority has been delegated by the Cognizant Secretarial Officer.)*

Approval recommended.

M. C. Wallace — *(Signature)* for W. D. Adams, Director, Research and Waste Management Division — *(Title)* 4/19/88 — *(Date)* OK GBL

11. SENSITIVE TRAVEL: Review by Head of DOE Field Organization. Has Field Security reviewed DOE F 1812.2 and completed DOE F 1812.3?

☐ YES ☐ NO

PART G—To be completed at Headquarters

12. REVIEW/COMMENTS BY DIRECTOR OF DIVISION OR OFFICE

(Signature) *(Title)* *(Date)*

13. COGNIZANT SECRETARIAL OFFICER

IF DOE EMPLOYEE TRAVEL ☐ IE Determination Received

IF SENSITIVE TRAVEL ☐ IE Determination Received ☐ ISA Determination Received ☐ OSS Determination Received

1128260

(Signature) *(Date)*

SEVENTH INTERNATIONAL SYMPOSIUM ON RADIOPHARMACEUTICAL CHEMISTRY

GRONINGEN, THE NETHERLANDS

4-8 JULI 1988

Chairman W. Vaalburg

ISRC V/V 88/80 Groningen, 16. 03. 1988

L. C. WASHBURN
MHSD DIV.
OAK RIDGES ASS. UNIV.
P. O. BOX 117
OAK RIDGE TN 37831
USA

Dear Authors,

It is a pleasure for me as Chairman to inform you that your paper

SYNTHESIS OF (18F)7-FLUOROHEPTYLAMINE AND TISSUE DISTRIBUTION STUDIES IN RATS
L. C. Washburn, T. T. H. Sun, B. L. Byrd and J. E. Crook
L. C. Washburn

has been accepted for oral presentation at the 7th International Symposium on Radiopharmaceutical Chemistry.

All oral presentations are alotted 12 minutes followed by 3 minutes for discussion.
Both slide (5cm x 5cm) and overhead projectors will be available for all oral sessions. For slides only single projection facilities.

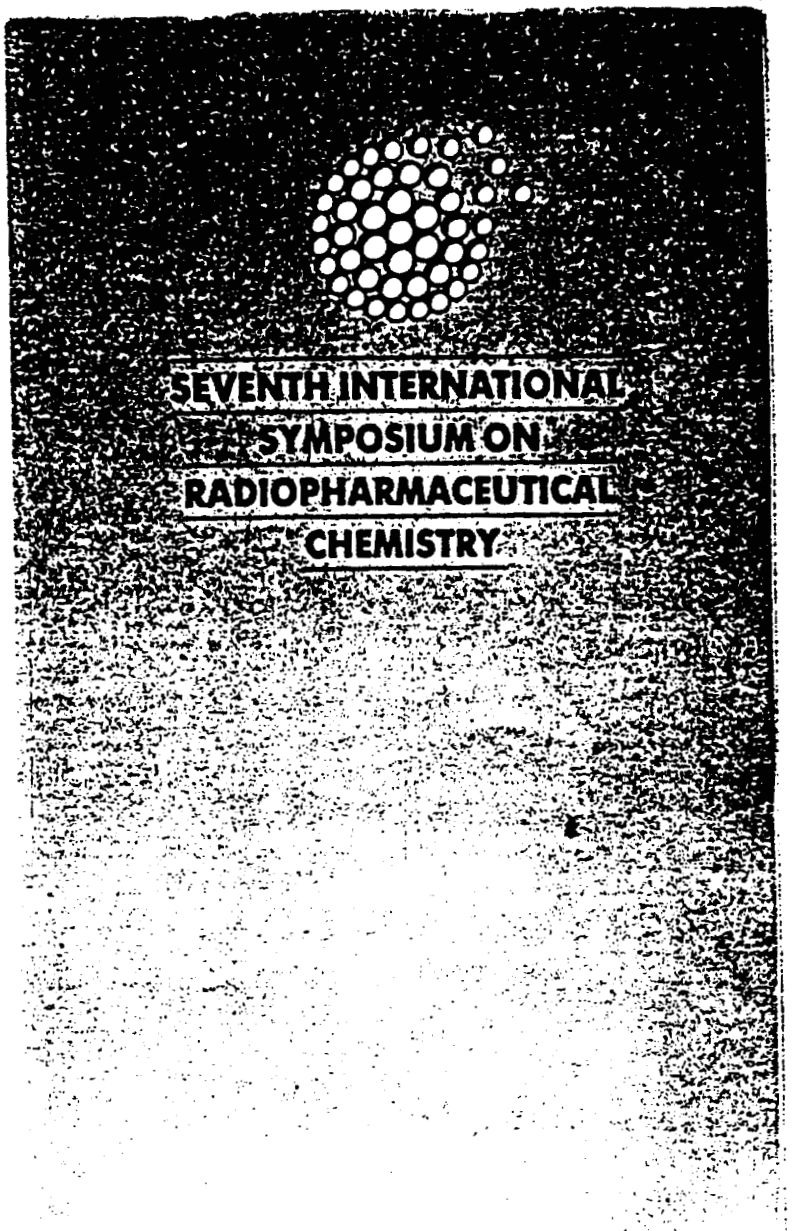
Looking forward to seeing you in Groningen.

Sincerely yours,

Willem Vaalburg, Ph. D.

1128261

University Hospital P.O. Box 30.001 9700 RB Groningen The Netherlands Tel. 050-612670 Telex 53942 AZGN NL



GRONINGEN, THE NETHERLANDS

4-8 JULI 1988

INVITATION

The Seventh International Symposium on Radiopharmaceutical Chemistry will be held from July 4-8, 1988, under the auspices of the University of Groningen and with the collaboration of the International Founding and Organizing Committee.

The scope of the Symposium will be similar to that of the previous meetings at Brookhaven, Oxford, St. Louis, Jülich, Tokyo and Boston and will include the following topics:

- design, preparation and quality control of radiopharmaceuticals;
- production of radionuclides for radiopharmaceuticals, including target design and automation of chemical processes;
- related chemical and biochemical studies.

Abstracts of the papers accepted for presentation will be published in The Journal of Labelled Compounds and Radiopharmaceuticals. Please also note that as in previous Symposia, papers describing purely clinical material will not be accepted.

The meeting will have no parallel oral sessions but will have simultaneous poster presentations. Attendance will be limited, with preference being given to the authors presenting papers.

This invitation contains the information for submission of abstracts, hotel reservations, transportation and the registration procedure. Please register and make your hotel reservation by completing the attached cards and returning them to the Symposium Secretariate and the Tourist Information Office respectively.

Local Organizing Committee

Willem Vaalburg, chairman
Anne M.J. Paans, co-chairman
Annie K. van Zanten, treasurer
Henk Beekhuis
Do A. Piers

Secretariate:
Annelies de Vries

General Organization:
Jitty Jaarsma

Department of Nuclear Medicine
University Hospital
University of Groningen
The Netherlands

International Founding and Organizing Committee

Monte Blau
Department of Radiology
Harvard Medical School
Boston, Massachusetts, USA

Dominique Comar
Service Hospitalier Frédéric Joliot
Orsay, France

William C. Eckelman
The Squibb Institute for Medical Research
New Brunswick, New Jersey, USA

Tatsuo Ido
Cyclotron and Radioisotope Center
Tohoku University
Sendai, Japan

Alun G. Jones
Department of Radiology
Harvard Medical School
Boston, Massachusetts, USA

INVITATION

Bengt Långström
University of Uppsala
Uppsala, Sweden

Wolfgang Maier-Borst
Institut für Nuklearmedizin, DKFZ
Heidelberg, FRG

David J. Silvester
MRC Hammersmith Hospital
London, UK

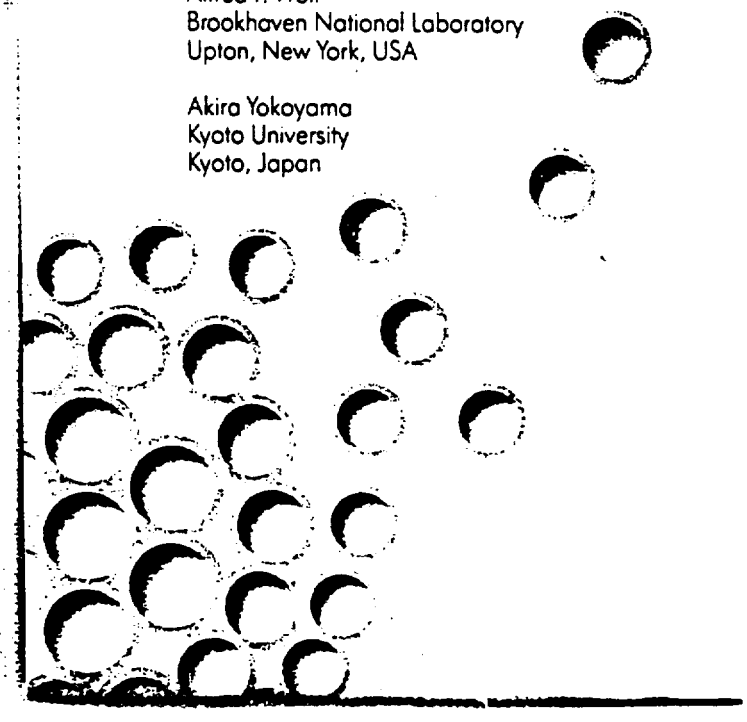
Gerhard Stöcklin
Institut für Chemie, KFA
Jülich, FRG

Willem Vaalburg
Department of Nuclear Medicine
University Hospital
Groningen, The Netherlands

Michael J. Welch
Edward Mallinckrodt Institute of Radiology
St. Louis, Missouri, USA

Alfred P. Wolf
Brookhaven National Laboratory
Upton, New York, USA

Akira Yokoyama
Kyoto University
Kyoto, Japan



Submission of Abstracts

Those who wish to submit scientific abstracts for review should do so directly to the member of the International Founding and Organizing Committee of their choice.
Abstracts should be no longer than three pages and should contain adequate supporting data, including tables, diagrams and references. The abstracts must be submitted in camera-ready format for eventual reproduction in both the Journal of Labelled Compounds and Radiopharmaceutical and the book of abstracts provided to all attendees More detailed intructions to authors accompany this announcement. For those who need early notification of acceptance in order to make travel plans, the deadline for receipt of abstracts is January 1, 1988. There will be immediate review of these abstracts and notification of the authors, although it will not be determined until all submissions are received wether the presentations will be oral or poster. All other abstracts must be submitted by January 24, 1988.

Registration

The attached registration card should be completed and returned before April 1, 1988. Registrations will start on the evening of Sunday July 3, 1988. The registration fee of DFl 300 is payable in Dutch guilders only and should be transferred to account 44.60.49.352 of 'Rijksuniversiteit Groningen' under reference code 'RPC-3224001' with the AMRO-bank in Groningen before April 1, 1988. After April 1, 1988 the registration fee will be increased to DFl 390.
The registration fee includes a copy of the book of abstracts, admission to all services, refreshments during the sessions, lunch on Monday through Friday, a party on Monday and the traditional midweek festivities.

General information
From the response to our first announcement we expect 300 scientists to participate in the symposium and about 170 papers to be submitted.

Accomodation

As the Symposium will be held during the holiday season, the Organizing Committee is facing some pressure as far as hotel rooms are concerned and you are therefore urgently requested to return your hotel reservation card as soon as possible - but no later than March 30, 1988 - to the

Tourist Information Office (V.V.V.)
Naberpassage 3
9712 JV Groningen
The Netherlands

Telephone: +3150 139700
Telex: 53138 vvgn nl.

who will deal with all hotel reservations. Hotel rooms can not be guaranteed for reservation cards received after this date.

Hotel categories are as follows:

A. - First class hotel Single room, bath, toilet	DFI 165 p.p.p.n.
B. - First/middle class hotel Single room, bath, toilet	DFI 125 p.p.p.n. ($65.88)
C. - Middle class/simple hotel	DFI 85 p.p.p.n. ($44.80)
D. - Simple hotel	DFI 45 p.p.p.n.

Please indicate on your reservation card the category of your 1st and 2nd preference. All hotels are situated near the Congress Center.

Rooms will be allocated on a first come, first served basis. As the number of single rooms is rather limited, it may be necessary to book participants into a double room and you are therefore requested to indicate on your reservation card the name of the participant you prefer to share your room with. (If no name is given, the Tourist Information Office will make the necessary reservations)

For low-budget travellers: there is a camping site in the city of Groningen, very close to the Congress Center. Please contact the Tourist Information Office of Groningen.

Transportation

By air:

There are regular flights between Amsterdam-Airport (Schiphol) and Groningen Airport (Eelde) except on Saturdays (no flights) and Sundays (one flight in the evening). Groningen Airport is situated about 10 km from the Congress Center and although public transport is available, a taxi is recommended (can be booked at Amsterdam Airport at the Netherlines' desk in the arrival hall).

KLM

Customs have to be cleared at Amsterdam Airport.

KLM Royal Dutch Airlines has been appointed Official Carrier for the Congress. KLM offices all over the world will meet your travel arrangement requirements.
For U.S. participants please call toll free 1-800-KLM-7777

By rail:

There is a direct railway connection from Amsterdam-Airport via Amsterdam Central Station, to Groningen Railway Station, every hour. No reservation is necessary. It takes about 3 h. to travel by train from Amsterdam to Groningen.
From the station of Groningen there are regular bus services to the Congress Center.
On Sunday evening transportation from the Congress Center to the various hotels will be provided.

Special events

An informal get-together party will be held on Sunday July 3 at the Congress Center from 17.00 - 21.00 h. in conjunction with registration.
On Monday evening you are invited to a reception by the Governor of Groningen at his residence.
No sessions are scheduled for Wednesday afternoon, July 6. A tour to the neighbouring province of Friesland, including a dinner, will be held during the afternoon and evening. A limited number of additional tickets may be obtained at registration. Please indicate on your registration card accordingly.
On Friday July 8, you are invited to a farewell lunch. A traditional Indonesian rice-buffet will be served.

General information about restaurants, sight seeing possibilities, entertainment, shopping etc. can be obtained at the information desk. Late night shopping is possible in Groningen on Thursday evening until 21.00 h.

General information:

Congress Center:
The Symposium will take place at the
'Martinihal Centrum'
Leonard Springerlaan 2
P.O. Box 8010
9702 KA Groningen
Telephone: +3150 262853
Telex: 5 35 48 mthal nl

The conference office/information desk will be located at the entrance of the Congress Center and will be open during conference hours as well as on Sunday July 3 from 16.00 - 21.00 h. for registration. Mail and/or messages for participants can be sent to this office.

For further information please contact:

Seventh International Symposium on Radiopharmaceutical Chemistry

c/o
University Hospital
Dept. of Nuclear Medicine
P.O. Box 30.001
9700 RB Groningen
The Netherlands

Telephone +3150 612670
Telex 53942 AZGN NL

Deadlines:
submission of abstract: January 24, 1988.
hotel reservation: March 30, 1988.
registration: March 30, 1988.
registration fee: March 30, 1988.